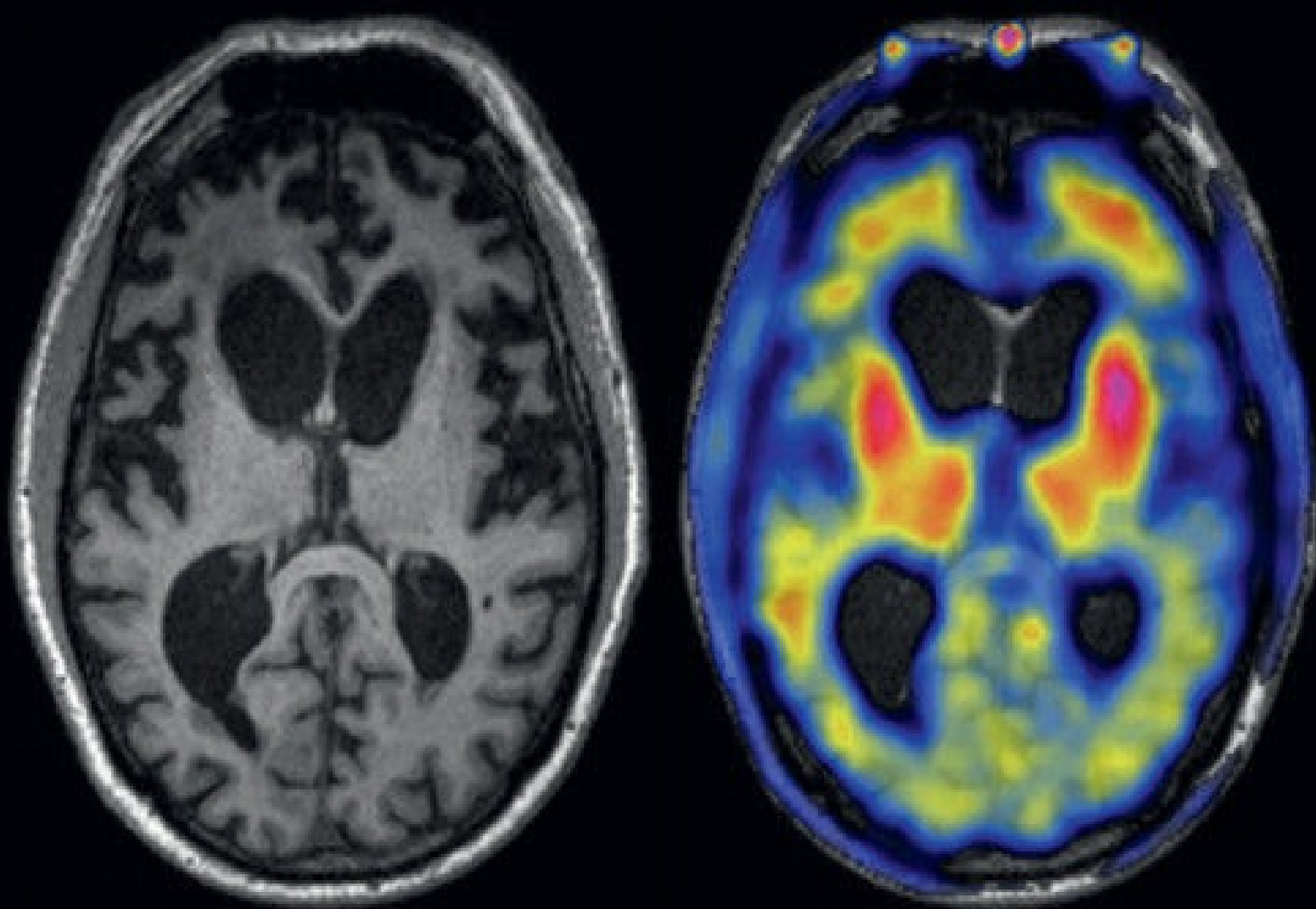


EDITED BY

Bradford C. Dickerson

SECOND EDITION

Hodges' Frontotemporal Dementia



CAMBRIDGE

Medicine

HODGES' FRONTOTEMPORAL DEMENTIA

Second Edition

Clinical and scientific interest in frontotemporal dementia (FTD) and related disorders is rapidly growing, as can be seen by increasing attendance at the International Meeting on FTD as well as the burgeoning literature. There remains an important need for a book broadly focused on clinical, pathologic, and scientific aspects of FTD. The Hodges book is the major textbook resource in the academic book literature on this topic. Major advances have occurred since its last publication. New clinical diagnostic criteria were published in 2011, new pathologic criteria have been developed, and several major genetic discoveries have been made. Thus, it is time for a new edition.

We aim to continue the outstanding tradition of this book, targeting an audience of specialist and generalist neurologists, psychiatrists, geriatricians, neuropsychologists, neuropathologists, and basic scientists in relevant fields. In addition to addressing cutting-edge topics of interest to faculty-level clinicians and scientists, the book contains material accessible enough for trainees in these fields.

Bradford C. Dickerson, MD (Harvard) is an Associate Professor of Neurology, Harvard Medical School, Director of the Frontotemporal Disorders Unit, and Co-Investigator at the Alzheimer's Disease Research Center, Massachusetts General Hospital, Boston, MA, USA.

HODGES' FRONTOTEMPORAL DEMENTIA

Second Edition

Edited by

Bradford C. Dickerson



CAMBRIDGE
UNIVERSITY PRESS



University Printing House, Cambridge CB2 8BS, United Kingdom

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning, and research at the highest international levels of excellence.

www.cambridge.org

Information on this title: www.cambridge.org/9781107086630

© Cambridge University Press 2016

This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First published 2007

Second edition 2016

Printed in the United Kingdom by TJ International Ltd. Padstow
Cornwall

*A catalogue record for this publication is available from the British
Library*

Library of Congress Cataloguing in Publication data

Hodges' frontotemporal dementia / edited by Bradford C. Dickerson. –
Second edition.

p. ; cm.

Frontotemporal dementia

Preceded by: Frontotemporal dementia syndromes / edited by John R.
Hodges. 2007.

Includes bibliographical references and index.

ISBN 978-1-107-08663-0 (hardback)

I. Dickerson, Bradford C., editor. II. Frontotemporal dementia syndromes. Preceded by (work): III. Title: Frontotemporal dementia.

[DNLM: 1. Frontotemporal Dementia. WM 220]

RC521

616.8'3 – dc23 2015010598

ISBN 978-1-107-08663-0 Hardback

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication, and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information which is in accord with accepted standards and practice at the time of publication. Although case histories are drawn from actual cases, every effort has been made to disguise the identities of the individuals involved. Nevertheless, the authors, editors, and publishers can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors, and publishers therefore disclaim all liability for direct or consequential damages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.

To my wife, Dr. Allison Berger, and our daughters, Molly and Lilly, who teach me every day the importance of open communication and connection, and the joy of loving kindness and shared curiosity, all of which makes our lives so much more than they would be without each other.

—Your loving husband and father

To all the individuals with illnesses who entrust their lives to me, their families and caregivers; I treasure our partnerships in the journeys we take as we try to make sense of living with these tragic diseases and do everything we can to fight back.

I dedicate this book to Dr. Leyla de Toledo-Morrell: pioneering neuroscientist, talented teacher, dedicated mentor, and loving friend and “grandmother.” Her passing in January 2015 left those of us lucky enough to know her with a deep hole in our lives.

—Brad Dickerson

Contents

[*List of contributors*](#)

[*Editor biographies*](#)

[*Foreword by Bruce Miller*](#)

[*Preface*](#)

Section 1: [Introduction to and brief history of FTD](#)

[1. Historical introduction to FTD](#)

John R. Hodges

[2. Overview of frontotemporal dementia and its relationship to other neurodegenerative disorders](#)

Paul McMonagle and Andrew Kertesz

Section 2: [Clinical phenotypes](#)

[3. Overview of frontotemporal dementia and the variety of its clinical presentations](#)

Matthew Jones and David Neary

[4. Behavioral variant frontotemporal dementia](#)

Katya Rascovsky

[5. Primary progressive aphasia](#)

Chiara Cerami and Stefano F. Cappa

[6. The FTD-ALS spectrum](#)

Thomas H. Bak and Sharon Abrahams

[7. Progressive supranuclear palsy and corticobasal degeneration in the FTD spectrum](#)

Barbara Borroni and Antonella Alberici

Section 3: [Approach to the diagnosis of FTD](#)

[8. Overview of clinical assessment of frontotemporal dementia syndromes](#)

Bradford C. Dickerson, Simon Ducharme, and Chiadi U. Onyike

[9. Neuropsychological assessment of frontotemporal dementia](#)

Teresa Torralva, Macarena Martinez Cuitiño, and Facundo Manes

[10. Imaging of frontotemporal dementia](#)

Jonathan D. Rohrer

[11. Cerebrospinal fluid biomarkers of frontotemporal lobar degeneration](#)

Nicolaas A. Verwey, Yolande A. L. Pijnenburg, and Philip Scheltens

[12. Genetic counseling for FTD](#)

Jill S. Goldman and Elisabeth McCarty Wood

Section 4: [Pathology and pathophysiology](#)

[13. Neuropathology of frontotemporal dementia and related disorders](#)

Manuela Neumann, Gabor G. Kovacs, and Ian R. A. Mackenzie

[14. Genetics of frontotemporal dementia and related disorders](#)

Marc Cruts and Christine Van Broeckhoven

[15. Pathophysiology and animal models of frontotemporal dementia](#)

Brian A. Warmus and Erik D. Roberson

Section 5: [Treatment](#)

[16. Functional disability and the impact of frontotemporal dementia in everyday life](#)

Claire M. O'Connor and Eneida Mioshi

[17. Practical management of frontotemporal dementia](#)

Edward D. Huey and Masood Manoochehri

[18. Pharmacologic therapy for FTD and related disorders: current options and future strategies](#)

Richard M. Tsai and Adam L. Boxer

[19. The family's perspective on FTD: enduring the journey, a force for change](#)

Susan Dickinson and Jill Shapira

[Index](#)

Contributors

Sharon Abrahams, PhD

*Chair of Neuropsychology & Consultant Clinical Neuropsychologist,
Department of Psychology & Euan MacDonald Centre for MND
Research at the University of Edinburgh, UK*

Antonella Alberici, MD

*Neurologist, Centre for Neurodegenerative Disorders, Neurology Unit,
University of Brescia, Brescia, Italy*

Thomas H. Bak, MD

*Department of Psychology & Euan MacDonald Centre for MND
Research at the University of Edinburgh, UK*

Barbara Borroni, MD

*Associate Professor of Neurology, Centre for Neurodegenerative
Disorders, Neurology Unit, University of Brescia, Brescia, Italy*

Adam L. Boxer, MD PhD

*Associate Professor of Neurology at the Department of Neurology,
University of California, San Francisco, CA, USA*

Stefano F. Cappa, MD

*Professor of Neuropsychology at the Vita-Salute San Raffaele University
and Director of the Neurology Department of San Raffaele Turro
Hospital, Milan, Italy*

Chiara Cerami, MD

*Neurologist and Research Fellow, Vita-Salute San Raffaele University
and San Raffaele Hospital, Milan, Italy*

Marc Cruts, PhD

Associate Professor at University of Antwerp, Belgium; Laboratory of Neurogenetics, Institute Born-Bunge; Senior Staff Scientist in the Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, VIB, Belgium

Bradford C. Dickerson, MD

Associate Professor of Neurology at Harvard Medical School, Boston, Director, Frontotemporal Disorders Unit, Co-investigator, Alzheimer's Disease Research Center, and Tom Rickles Endowed Chair in Primary Progressive Aphasia, Massachusetts General Hospital, Charlestown, MA, USA

Susan Dickinson, MS CGC

Executive Director at the Association for Frontotemporal Degeneration, Radnor, PA, USA

Simon Ducharme, MD, MSc

Assistant Professor Department of Psychiatry, Montreal Neurological Institute and McGill University Health Centre, Montreal, Quebec, Canada

Jill S. Goldman, MS MPhil CGC

Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA

John R. Hodges, MD FRCP FRACP F Med Sci

Professor of Cognitive Neurology, Neuroscience Research Australia and University of New South Wales, NSW, Australia

Edward D. Huey, MD

Herbert Irving Assistant Professor of Psychiatry and Neurology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, The Gertrude H. Sergievsky Center, Columbia University, New York, NY, USA

Matthew Jones, MD MRCP

Cerebral Function Unit, Greater Manchester Neurosciences Centre, Salford Royal Foundation Trust and the Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK

Andrew Kertesz, MD FRCPC

Professor of Neurology at the Department of Neurology, University of Western Ontario, London, Ontario, Canada

Gabor G. Kovacs, MD PhD

Associate Professor and Leader of Working Group Neurodegenerative Diseases at the Institute of Neurology, Medical University of Vienna, Vienna, Austria

Ian R. A. Mackenzie, MD FRCPC

Professor of Pathology and Laboratory Medicine at the University of British Columbia, Consultant Neuropathologist and Head of Division of Neuropathology at Vancouver General Hospital, Vancouver, British Columbia, Canada

Facundo Manes, MD PhD

Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina; Institute of Neuroscience, Favaloro University, Buenos Aires, Argentina; UDP-INECO Foundation Core on Neuroscience (UIFCoN), Diego Portales University, Santiago, Chile; Australian Research Council (ACR) Centre of Excellence in Cognition and its Disorders; and the National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina

Masood Manoochehri, BA

Taub Institute for Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University, New York, NY, USA

Macarena Martinez Cuitiño, PhD

Speech Pathologist, Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina; Institute of Neuroscience, Favaloro University, Buenos Aires, Argentina; and the University of Buenos Aires, Buenos Aires, Argentina

Elisabeth McCarty Wood, MS CGC

Center for Neurodegenerative Disease Research at the University of Pennsylvania, Philadelphia, PA, USA

Paul McMonagle, MD FRCP FRCPI

Consultant Neurologist at the Department of Neurology, Royal Victoria Hospital, Belfast, N. Ireland

Eneida Mioshi, OTR PhD

Department of Psychiatry, University of Cambridge, Cambridge, UK

David Neary, MD FRCP

Cerebral Function Unit, Greater Manchester Neurosciences Centre, Salford Royal Foundation Trust and the Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK

Manuela Neumann, MD

Chair of the Department of Neuropathology at the Medical Faculty of the Eberhard Karls University of Tübingen and Medical Director of the Department of Neuropathology, University Hospital Tübingen, Germany

Claire M. O'Connor, MOT (Hons)

Ageing, Work & Health Research Unit, University of Sydney, NSW, Australia

Chiadi U. Onyike, MD MHS

Department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins School of Medicine, Baltimore, MD, USA

Yolande A. L. Pijnenburg, MD PhD

Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, the Netherlands

Katya Rascovsky, PhD

Department of Neurology and Frontotemporal Degeneration Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Erik D. Roberson, MD PhD

*Center for Neurodegeneration and Experimental Therapeutics,
Departments of Neurology and Neurobiology, University of Alabama at
Birmingham, Birmingham, AL, USA*

Jonathan D. Rohrer, MD

*Honorary Consultant Neurologist at the National Hospital for Neurology
and Neurosurgery, MRC Clinician Scientist at UCL Institute of
Neurology, Queen Square, London, UK*

Philip Scheltens, MD PhD

*Alzheimer Center and Department of Neurology, VU University Medical
Center, Amsterdam, the Netherlands*

Jill Shapira, RN PhD

UCLA Behavioral Neurology Clinic, Los Angeles, CA, USA

Teresa Torralva, PsyD

*Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina;
Institute of Neuroscience, Favaloro University, Buenos Aires, Argentina;
UDP-INECO Foundation Core on Neuroscience (UIFCoN), Diego
Portales University, Santiago, Chile; and Australian Research Council
(ARC) Centre of Excellence in Cognition and its Disorders*

Richard M. Tsai, MD MBA

*Clinical Instructor at the Department of Neurology, University of
California, San Francisco, CA, USA*

Christine Van Broeckhoven, PhD DSc

*Professor of Molecular Biology and Genetics at the University of
Antwerp, Belgium; Research Director of the Laboratory of Neurogenetics
at the Institute of Born-Bunge; Director of the Department of Molecular
Genetics at VIB, and Head of Neurodegenerative Brain Diseases
Research group*

Nicolaas A. Verwey, MD PhD

*Neurologist at the Medical Centre Leeuwarden, and formerly at the
Neurology Department/Alzheimer Center, VU Medical Center,
Amsterdam, the Netherlands*

Brian A. Warmus, PhD

*Center for Neurodegeneration and Experimental Therapeutics,
Departments of Neurology and Neurobiology, University of Alabama at
Birmingham, Birmingham, AL, USA*

Editor biographies



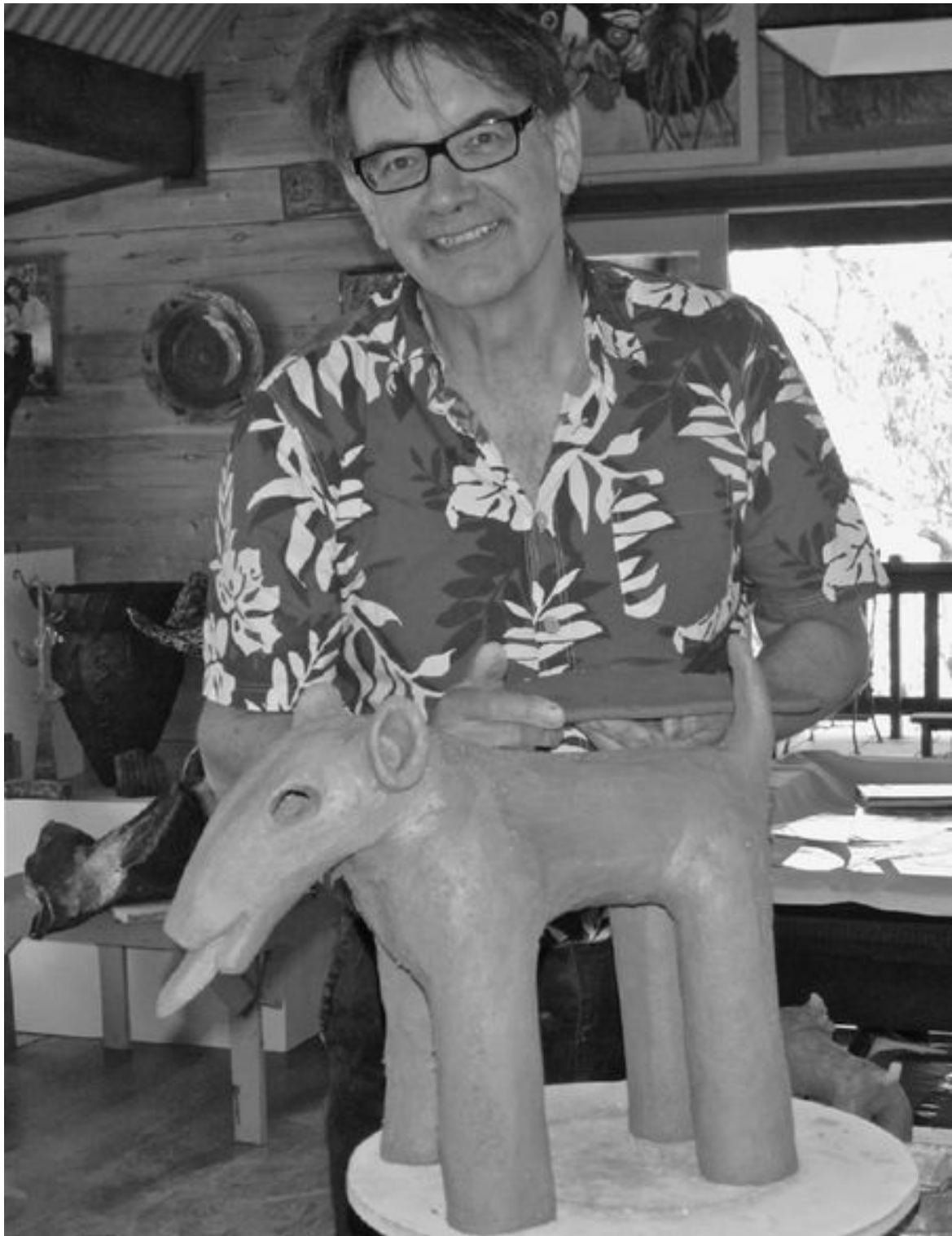
Bradford C. Dickerson, MD MMSc

Brad Dickerson, MD, is a behavioral neurologist and neuroscientist at Harvard Medical School and Massachusetts General Hospital (MGH) in Boston, Massachusetts. He is the Director of the Massachusetts General Hospital Frontotemporal Disorders Unit (<http://www.ftd-boston.org>) and Neuroimaging Lab in Boston, and the Tommy Rickles Endowed Chair in Primary Progressive Aphasia Research at MGH. He is also a staff behavioral neurologist in the MGH Memory Disorders Unit and a co-investigator in the Alzheimer's Disease Research Center. He is an Associate Professor of Neurology at Harvard Medical School. He completed undergraduate studies in biomedical engineering at Southern Methodist University in Dallas, medical school at University of Illinois at Chicago College of Medicine, and neurology residency at MGH and Brigham and Women's Hospital in Boston; he did fellowships in neuroimaging at the Martinos Center for Biomedical Imaging and in behavioral neurology at Brigham and Women's Hospital in Boston.

Dr. Dickerson runs a busy weekly clinic caring for patients with various forms of cognitive impairment and dementia, as well as providing training for clinical and research fellows. His research has focused primarily on the use of quantitative structural and functional neuroimaging techniques to understand the neurobiology of Alzheimer's disease, primary progressive aphasia, frontotemporal dementia, and other dementias, and on the relationships between imaging measures and behavior. He also investigates the neural substrates of changes in memory, affect, and other abilities in healthy young adults and in normal aging. He has taught widely to many audiences, and currently co-directs the annual Harvard Dementia CME course and the annual American Academy of Neurology Primer of Behavioral Neurology course. He has published more than 90 articles in peer-reviewed scientific journals as well as many book chapters, and has

edited one book, *Dementia: Comprehensive Principles and Practice* (Oxford University Press).

He is the Principal Investigator on multiple NIH and foundation grants studying aging and dementia, and serves on the medical advisory boards for the Association for Frontotemporal Degeneration and the Massachusetts chapter of the Alzheimer's Association. He has won a number of awards, including the prestigious American Academy of Neurology Norman Geschwind Award in Behavioral Neurology and Honorable Mention for the Schwartz Center Award for Compassionate Care. When not practicing neurology, Brad enjoys spending time with his family and playing drums in his rock band with Allison...



John Hodges, MD FRCP FRACP FMed Sci

John is Professor of Cognitive Neurology based at Neuroscience Research Australia where he co-directs the Frontotemporal Dementia

Research Group (FRONTIER <http://www.ftdrg.org>) and is a Principal Investigator of a NHMRC Program.

John qualified in Medicine from London University with honours (1975) and undertook periods of psychiatric and neurologic training in Southampton, Oxford, and San Diego and obtained his MD in 1988. From 1997 to 2007 he was the MRC Professor of Behavioural Neurology with joint appointments in the Department of Clinical Neuroscience at Addenbrooke's Hospital and the MRC Cognition and Brain Sciences Unit, Cambridge. He moved to Sydney in 2007 as an ARC Federation Fellow and established FRONTIER with support from the ARC and NHMRC.

He has a long-standing interest in many aspects of cognition, particularly in the context of neurodegenerative disorders. His current research focuses on aspects of frontotemporal dementia. He is the author of over 450 journal articles and five books including *Cognitive Assessment for Clinicians* (Oxford University Press, 2007), *Early-Onset Dementia* (Oxford University Press, 2001), and *Frontotemporal Dementia Syndromes* (Cambridge University Press, 2007).

Foreword

First described in 1892, frontotemporal dementia (FTD) and related disorders are finally gaining public and scientific interest as the decades of labeling every cognitive disease of aging “Alzheimer's disease” are dwindling. FTD is a devastating disease for patients and caregivers that usually begins to be noticed in people in their 40s, 50s, and 60s, while people are expected to be active participants in career, family, and community. This young age of onset combined with a commonly psychiatric presentation means that there are often many alternate diagnoses proposed before the correct one is identified. Patients and families often go through years of searching for the correct diagnosis and understanding what is happening. Unfortunately by the time an accurate diagnosis is made, oftentimes the supportive relationships that hold families together are already deeply strained owing to the exceptionally difficult behaviors, poor judgment, and personality changes frequently seen in patients with FTD. This situation can be dangerous for patients with a progressive neurodegenerative disease if they are left without any support before the disease is identified.

With new technologies and clinical insights, patient diagnoses are becoming more precise, and scientists are working to understand the molecular drivers of each type of FTD spectrum disorder. This rigorous approach is bringing us closer to treatments than we have ever been, and a treatment for FTD could unlock treatments for Alzheimer's disease, Parkinson's disease, Creutzfeldt–Jakob disease, and others. The active

search for reliable biomarkers is a hot area of research now. Such biomarkers could provide an objective diagnosis much earlier when treatment could start before symptoms emerge. These biomarkers could also provide measures of treatment success in clinical trials, which could help identify a cure.

Regular international meetings bring together scientists and clinicians from each continent to share the discoveries and challenges seen in diverse cultures and geographies. This worldwide sharing also crosses disciplinary boundaries to include neurologists, psychiatrists, geriatricians, neuropsychologists, neuropathologists, nurses, genetic counselors, and basic scientists to provide a truly broad understanding of the changes in the brain in FTD. This comprehensive review of FTD brings together the latest findings from the rich international community of researchers growing larger each year. Covering the clinical phenotypes, diagnostic issues, pathology, and treatment, the editor of this edition has brought these discoveries together in one place. This outstanding edition is a must-read for anyone interested in dementia.

Bruce L. Miller, MD

*A.W. and Mary Margaret Clausen Distinguished Professor in
Neurology*

Director, Memory and Aging Center

Joint Appointment in Psychiatry

*University of California at San Francisco School of Medicine, San
Francisco, CA, USA*

Preface

I am honored to serve as the editor of *Hodges' Frontotemporal Dementia* (second edition), which I have worked to refine as a clinically oriented book aiming to provide a comprehensive reference for the frontotemporal dementia (FTD) spectrum of neurodegenerative diseases. When I was asked to carry on the tradition of this volume started by Professor John Hodges, I wanted to honor the tradition John started in the first edition of this book while expanding it to include the many new insights and advances by the broad international FTD clinical and research community that have developed over the past eight years since its original publication. I named the revision of this book after John to honor his groundbreaking clinical, research, and teaching/mentorship contributions to the fields of FTD, primary progressive aphasia (PPA), memory, behavioral neurology, and neurodegenerative disease research.

The first edition of this book has filled a very special niche, and I hope the second edition will continue in this vein. The FTDs are rare but important diseases that are slowly yielding their secrets to the international community of investigators dedicated to unlocking them. It is remarkable to witness the growth of the diverse but strongly collaborative group of clinicians and scientists around the world, and the ways in which patients and families join efforts to advance our collective knowledge of these diseases and attempts to treat them.

Although I had talked with and learned from patients and family members suffering with “Pick's disease” in the early 1990s when I worked

at the Alzheimer's Association, it was not until 2002 that I diagnosed and treated my first patient, Joe J., as a neurology resident. From that time forward, with the encouragement and support of colleagues and mentors, I have been captivated by the special needs of patients and families living with these mysterious illnesses – not to mention the fascinating science of these diseases – and I vowed to try to contribute to efforts to improve their plight. As my interest deepened in PPA and semantic memory impairment, I started the Massachusetts General Hospital (MGH) PPA Program in the fall of 2007 with Daisy Sapolsky, who was introduced to me by my good friend and colleague (and her future husband) Dr. Leigh Hochberg. Drs. David Caplan, Marsel Mesulam, and Sandy Weintraub, along with Paige Nalipinski and Joyce Shapiro Gordon (senior speech pathologists at MGH), helped us start our clinical research program in PPA. Once we “hung our shingle,” we were fortunate to have many colleagues who referred patients and families to our program. As we worked with increasing numbers of people, I began turning a substantial portion of my effort to PPA, FTD, and related disorders. Dr. Anne Young, Chief of Neurology at MGH, and Drs. John Growdon and Brad Hyman enthusiastically supported my proposal to start a specialized clinical and research unit dedicated to FTD, and the MGH FTD Unit was born in the fall of 2008. We have since had the good fortune of working with many wonderful patients, families, and colleagues, and have received funding from the NIA, NINDS, NIMH, Alzheimer's Association, and Association for FTD, as well as multiple philanthropic organizations and generous families; we have evaluated and treated more than 300 patients over the past eight years.

On November 13, 2014, shortly after the 9th International Conference on FTD, we held our fourth Boston-area MGH FTD Unit Caregiver Education and Support day. As I talk with my colleagues around the world, we share similar stories of the power that programs such as this offer.

Bringing together the community of patients, families, other loved ones, clinicians, researchers, and other dedicated professionals, programs like this one help us realize how critical it is to have dedicated interdisciplinary teams working on FTD and networks of caring individuals putting effort toward improving the lives of those affected by these illnesses. As most people in this community recognize, this is a defining feature of the international FTD research and clinical community – it is a closeknit, collaborative “family.”

This book is designed to improve knowledge about the FTD spectrum and competence in its clinical management, hopefully translating into improved early detection, accurate diagnosis, and compassionate comprehensive care and treatment. Written primarily for clinicians, this volume takes a multidisciplinary approach to understanding FTD and is aimed toward neurologists, psychiatrists, geriatricians, psychologists, genetic counselors, speech pathologists, nurse specialists, internists, primary care physicians, social workers, occupational and physical therapists, clinical pharmacists, research scientists, and other health professionals involved in the diagnosis, management, and investigation of FTD and related illnesses.

The first part of the book provides an historical introduction by John Hodges and a broad overview of the complex relationships between these illnesses by Paul McMonagle and Andy Kertesz. The second part of the book delves more deeply into clinical phenotypes, with sections on each of the major syndromes by Matthew Jones and David Neary (overview), Katya Rascovsky (behavioural variant FTD), Chiara Cerami and Stefano Cappa (PPA), Sharon Abrahams and Tom Bak (the FTD-ALS spectrum), and Barbara Borroni and Antonella Alberici (progressive supranuclear palsy and corticobasal degeneration). The next section reviews a clinical approach to the diagnostic assessment of FTD spectrum illnesses, with

chapters by Chiadi Onyiki, Simon Ducharme, and myself (overview of clinical assessment), Teresa Torralva, Macarena Martinez Cuitiño, and Facundo Manes (neuropsychology), Jonathan Rohrer (imaging), Nick Verwey, Yolande Pijnenburg, and Philip Scheltens (cerebrospinal fluid biomarkers), and Beth McCarty Wood and Jill Goldman (genetic counseling). The next section then provides an up-to-date survey of neuropathology by Ian Mackenzie, Gabor Kovacs, and Manuela Neumann, genetics by Marc Cruts and Christine Van Broeckhoven, and pathophysiology and animal models by Brian Warmus and Erik Roberson. Finally, the last section reviews treatment of FTD, including quantification of impairment in everyday life by Claire O'Connor and Eneida Mioshi, practical management by Ted Huey and Masood Manoochchhri, current and future pharmacologic therapy by Richard Tsai and Adam Boxer, and the family's perspective by Susan Dickinson and Jill Shapira.

Besides providing cutting-edge reviews of the literature, one of my goals was to obtain personal perspectives and “clinical pearls” by internationally respected leaders in the field. I hope that specialists will find this book useful as an up-to-date reference work, while less specialized clinicians will take away valuable principles useful in daily clinical practice, and trainees at all levels will enjoy an opportunity to appreciate the broad array of disciplines that FTD touches. Ultimately, FTD will be conquered by the concerted efforts of this international army of experts from across many fields of basic and clinical neuroscience, in close partnership with patients and families, advocacy and support communities, funding agencies and philanthropists, and industry groups.

I greatly appreciate the efforts of the contributors, who took time out from their usual activities to distill their knowledge for this book. Nicholas Dunton, Kirsten Bot, and Charlotte Thomas at Cambridge University Press were invaluable in helping me to develop this project and nurture it to

completion. In addition, I would like to thank Susan Dickinson, Nadine Tatton, Sharon Denny, Matt Sharp, and Helen Ann Comstock, as well as the AFTD board members, whose tireless efforts on behalf of the FTD community through the Association for FTD are outstanding. In addition, I treasure the partnership of colleagues from the Massachusetts/New Hampshire chapter of the Alzheimer's Association, including Paul Raia, Jerry Flaherty, Lindsay Brennan, Susan Rowlett, Nicole McGurin, Brooke Patterson, Nancy Nichols, Lenore Jackson-Pope, and Jim Wessler. I would like to extend special thanks to my mentors and colleagues who have sculpted my thinking in so many ways: Tony Phelps, Sheryl Williams, Leyla deToledo-Morrell, Marsel Mesulam, Sandy Weintraub, Mario Mendez, Martin Samuels, Marilyn Albert, Reisa Sperling, Kirk Daffner, Deborah Blacker, Brad Hyman, John Growdon, David Caplan, Jeremy Schmahmann, Bruce Price, Keith Johnson, Anne Young, Merit Cudkowicz, Bruce Rosen, Matthew Frosch, Steve Haggarty, Jim Gusella, Rudy Tanzi, Mykol Larvie, Maurizio Fava, Paige Nalipinski, Joyce Shapiro Gordon, Janet Sherman, Doreen Rentz, Barbara Maxam, Randy Buckner, Daphne Holt, Nikos Makris, and Lisa Feldman Barrett. Special thanks to Liz and George Krupp for your generous support through your Tom Rickles fund in honor of your dear brother, and also to Marie and Brandt Henderson and many other individuals who have contributed critical financial support to our program. Many mentors and colleagues in the broader FTD community have provided incredibly generous inspiration, encouragement, and wise counsel as I have developed our FTD clinical research program, including Bruce Miller, Marsel Mesulam, Sandy Weintraub, Dino Ghatti, Bill Seeley, Marliu Gorno-Tempini, Emily Rogalski, Howie Rosen, Adam Boxer, Brad Boeve, Dave Knopman, Jon Rohrer, Kate Rankin, Gil Rabinovici, Katya Rascovsky, Murray Grossman, Tiffany Chow, Mario Mendez, and John Hodges. I am very lucky to have the partnership of several special people in the Boston-

area FTD community, including Emily Levy, Barbara Neufeld, Amy Almeida, Genevieve Wanucha, and especially Katie Brandt. The ADRC Longitudinal Cohort team has been critical to our efforts, including Jeanette Gunther, Kelly Hennigan, Larissa Collins, Frannie Hatling, Amy Zoller, Kyleen Swords, Jillian Kizielewicz, and Jon Hirschberger. So much of our clinical and research effort has been carried out by outstanding fellows, students, and other trainees, including Daisy Hochberg, Kimiko Domoto-Reilly, Luce Pellerin, Liang Wang, Stephane Poulin, Kristin Lindquist, Maria Gendron, Belen Pascual, Kevin Bickart, Yakeel Quiroz, Mandana Modirrousta, Joan Camprodon, Chenjie Xia, Mark Eldaeif, David Perez, Ryan Darby, Simon Ducharme, Mia Minen, Elena Ratti, Megan Quimby, Claire Cordella, Rani Sarkis, Sara Mitchell, Jaya Padmanabhan, Abid Qureshi, and Tamar Gefen. Special thanks to my good friends and colleagues David Wolk and Ali Atri. Finally, I am immensely grateful for the dedication of many wonderful individuals in the FTD Unit and other collaborators, including Daisy Hochberg, Kimiko Domoto-Reilly, Scott McGinnis, Diane Lucente, Akram Bakkour, Aly Negreira, Mike Brickhouse, Mark Hollenbeck, Mike Stepanovic, Megan Quimby, Christina Caso, Katie Kelly, Sara Makaretz, Liz Lynch, and especially our stellar “front office” team, including Jackie Mazzie, Karolina Ballester, Ayana Cole, Brianna O'Connell, and Rose Gallagher.

Most important, for their love, support, and inspiration, I thank my family, including Allison Berger, Molly Dickerson, Lilly Dickerson, Jeannae Dickerson, Jim Dickerson, Sarah Dickerson, Lewis Berger, Ileana Berger, and Stacie, Isabel, Avery, Vivian, and Karl Siebrecht.

And I want to give special acknowledgment to the many patients, family members, caregivers, and others who have entrusted me with intimate details from your lives and the humbling opportunity to learn from and with you during this journey, and to offer you the opportunity to join

forces in our fight against these terrible diseases. I will do my best to help ensure that your contributions help pave the way toward deeper knowledge of these diseases and ultimately better treatments. We strive toward a world without FTD, and while we work toward a cure, we give the best care we can.

Section 1



Introduction to and brief history of FTD

Chapter 1

Historical introduction to FTD



John R. Hodges

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

Over the two past decades there have been considerable advances in our understanding of the major neurodegenerative diseases producing focal cognitive deficits, most commonly referred to collectively as either Pick's disease or, more recently, frontotemporal dementia (FTD). These advances have come from the fields of neuropsychology, neuropsychiatry, neuroimaging, neuropathology, and molecular genetics. Unfortunately, most non-experts' ability to follow these developments has been hindered by the confusing plethora of terms which have been used. Central to the problem is a lack of clarity concerning the level of description (clinical syndrome versus clinicopathologic entity versus specific histologic diagnosis) and the poor concordance between these levels. In other words, while some labels denote a clinical syndrome without specific histologic implications (e.g.,

progressive aphasia, semantic dementia, or dementia of frontal type), others denote specific neuropathologic entities (e.g., Pick's disease, familial tauopathy, ubiquitin-inclusion disease), hybrid clinicopathologic entities (frontotemporal dementia), or even specific genetic disorders (e.g., chromosome 17-linked frontotemporal dementia with parkinsonism [FTDP-17]). The resurgence of interest in these disorders and the differences in opinion over terminology are well illustrated by the titles of the previous books published on the topic: *Pick's Disease and Pick's Complex* (Kertesz and Munoz, [1998](#)), *Frontotemporal Dementia* (Pasquier *et al.*, [1996](#)), and *Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia* (Snowden *et al.*, [1996b](#)).

The aims of this introductory chapter are to review the evolution of the terms used to describe this spectrum of disorders, to highlight recent advances and areas of continuing controversy, and to set the scene for the rest of the book. While my own preference has always been to use the term Pick's disease for this group of disorders – partly because this term is more readily understood by carers and parallels our use of the label Alzheimer's disease – the tide of medical opinion turned in favor of FTD in the late 1990s. We have, therefore, adopted this general label within which we distinguish two main clinical variants: behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA) with further subclassification of the aphasic cases. The sections that follow describe the meandering route that led to the adoption of these terms. The chapter draws heavily upon my own experience of more than 500 patients assessed in Cambridge and in Sydney over the past 20 years and has been updated since the first edition of the book to reflect areas of evolution and change.

What did Arnold Pick actually describe?

In 1892 Arnold Pick (Girling and Berrios, [1994](#)), working in Prague, reported a 71-year-old man with progressive mental deterioration and unusually severe aphasia who at post-mortem had marked atrophy of the left temporal lobe. Twelve years later in 1904 he published his landmark paper (“On the symptomatology of left-sided temporal lobe atrophy”) in which he described three further cases (Girling and Berrios, [1997](#)). The first, a 58-year-old woman (Josephina) had a two-year history characterized by a striking loss of memory for names (amnesic aphasia) culminating in almost complete loss of speech and accompanied by changes in personality. She deteriorated rapidly and at post-mortem, two years after presentation, Pick observed asymmetric temporal lobe atrophy involving particularly the inferior and middle gyri (i.e., not Wernicke's area). Methods of staining brain sections were not available at that time and Pick was able to make observations on the macroscopic pathology only. The other two cases were clinically similar, except that case three had the complication of cerebral syphilis, preventing firm conclusions about the cause of the focal brain atrophy. Pick wanted to draw attention to the fact that progressive brain atrophy may lead to symptoms of focal disturbance (in this instance aphasia) through local accentuation of the disease process. He also made specific and, as we will see below, highly perceptive predictions regarding the role of the mid temporal region of the left hemisphere in the representation of word meaning. It was only in his later publication that Pick turned his attention to bilateral frontal atrophy with resultant behavioral disturbance.

Pick made major contributions which have sadly been rather overlooked in recent years. Current classifications have also relegated him to a minor role but several points should be emphasized: (1) Pick's primary interest was the language and behavioral disorder, particularly the clinico-anatomical correlates of aphasia; (2) he did not claim to have discovered a new disease, merely novel phenomena arising from asymmetric

degeneration; (3) two of the major syndromes now included under the rubric of FTD (bvFTD and semantic dementia) were clearly described by Pick; (4) he did not describe distinct histopathologic changes in his patients with focal atrophy.

The histologic abnormalities associated with Pick's disease were, in fact, described a few years later by Alzheimer ([1911](#)) who recognized changes distinct from those found in the form of cerebral degeneration later associated with his name. Alzheimer recognized both argyrophilic intracytoplasmic inclusions (Pick bodies), and diffusely staining ballooned neurons (Pick cells) in association with focal lobar atrophy. It is interesting to note that a comprehensive review of 20 patients from the literature with aphasia due to focal lobar atrophy written soon after Alzheimer's description (Mingazzini, [1913](#)) did not use the label Pick's disease. Onari and Spatz ([1926](#)) were among the first to use the eponym Pick's disease but Carl Schneider ([1927](#), [1929](#)) is probably most responsible for its introduction. Unfortunately, however, he concentrated on the frontal lobe component of the syndrome and began the neglect of the temporal lobe syndromes associated with focal atrophy that continued for at least half a century. He distinguished three clinical phases – the first characterized by impaired judgment and behavior, the second by focal symptoms, and the third by generalized dementia. Many papers describing similar cases appeared in the 1930s and 1940s (e.g., Ferraro and Jervis, [1940](#); Löwenberg and Arbor, [1936](#); Löwenberg *et al.*, [1939](#); Neumann, [1949](#); Nichols and Weigner [1938](#)) which mainly focused on the frontal lobe aspects of the disorder. Given the more recent genetic discoveries related to the gene for tau protein, special mention should be made of the large Dutch family first reported by Sanders *et al.* ([1939](#)) and then again by Schenk ([1951](#)). These families were central to developments in the 1990s when linkage to the tau gene region on chromosome 17 was established by

workers in the USA (Wilhelmsen *et al.*, [1994](#)) and Europe (Heutink *et al.*, [1997](#)).

With the general waning of interest in the cognitive aspects of neurology in the English-speaking world, interest in focal dementia syndromes faded, as reflected by the dearth of clinical papers in the neurologic literature after the Second World War. Indeed, many authors went as far as to claim that Alzheimer's and Pick's disease were clinically indistinguishable in life (Kamo *et al.*, [1987](#); Katzman, [1986](#)). The focus of interest in English language publications became the neuropathology, and latterly the genetics, of these conditions. This resulted in a gradual change in the criteria for Pick's disease, which evolved to include the necessity for specific pathologic changes (i.e., focal atrophy with Pick cells and/or Pick bodies). In continental Europe, however, there remained a strong interest in the clinical phenomena of the dementias; Pick's remained an *in vivo* diagnosis based on a combination of clinical features suggestive of frontal and/or temporal lobe dysfunction and focal lobar atrophy (e.g., Mansvelt, [1954](#); Tissot *et al.*, [1975](#), [1985](#)).

This controversy continues and has contributed to the adoption of the many labels to describe patients with the clinical syndrome of progressive frontal or temporal lobe degeneration.

Rediscovering Pick's disease: from dementia of the frontal type and progressive aphasia to frontotemporal dementia

A renaissance of interest in the focal dementias began in the 1980s. Workers from Lund, Sweden (Brun, [1987](#); Gustafson, [1987](#)) reported on a large

series of patients with dementia and found that of 158 patients studied prospectively who came to post-mortem, 26 had evidence of frontal lobe degeneration. Since only a small proportion had Pick cells and Pick bodies – the remainder had very similar findings but without specific inclusions (i.e., focal lobar atrophy with severe neuronal loss and spongiosis) – the Lund group preferred to adopt the term “frontal degeneration of non-Alzheimer type.” At approximately the same time, Neary and co-workers in Manchester (Neary *et al.*, [1986](#)) began a series of important clinicopathologic studies of patients with presenile dementia. They, likewise, found a high proportion of cases with a progressive frontal lobe syndrome who had neither specific changes of Alzheimer's disease (plaques and tangles) nor specific inclusion pathology. They introduced the term “dementia of frontal type.” Over the next few years other groups described very similar cases under the labels “frontal lobe degeneration” (Miller *et al.*, [1991](#)) and “dementia lacking distinct histologic features” (Knopman *et al.*, [1990](#)). These papers were important in defining the key clinical features associated with progressive frontal lobe degeneration, notably: alterations in social conduct, inhibitory control, sexual behavior, appetite; ritualized and stereotypic behaviors; reduced empathy; and apathy.

In more recent classifications these patients have been given either the general label of FTD (as distinct from progressive aphasia and semantic dementia) or alternatively frontal variant FTD and more recently bvFTD. Key advances have been the development of carer-based interview schedules or questionnaires such as the Neuropsychiatric Inventory (NPI; Cummings *et al.*, [1994](#)), the Frontal Behavioral Inventory (FBI; Kertesz *et al.*, [2000](#)), and the Cambridge Behavioural Inventory (CBI; Bozeat *et al.*, [2000](#)). It has become apparent that conventional frontal lobe tests based largely on executive abilities (planning, set-shifting, problem-solving) are not very sensitive to the beginnings of this behavioral form of FTD. A range

of exciting recent research has focused on ways of measuring the alterations in social conduct, theory of mind, emotion processing, and complex decision-making (Bertoux *et al.*, [2012](#); Gregory *et al.*, [2002](#); Keane *et al.*, [2002](#); Kumfor and Piguet, [2012](#); Kumfor *et al.*, [2013](#); Lough *et al.*, [2006](#); Rahman *et al.*, [1999](#); Rankin *et al.*, [2003](#); Torralva *et al.*, [2007](#)). It had been long assumed that the orbital cortex bears the brunt, particularly in the early stages of the disease, but recent quantitative imaging work has emphasized rather the role of the mesial surface. Moreover, some of the symptoms typically regarded as “frontal” in nature may, in fact, be secondary to amygdala or insula damage. Studies attempting to relate individual clinical features to site(s) of brain dysfunction using structural or functional imaging are in their infancy (Hornberger *et al.*, [2011](#); Kloeters *et al.*, [2013](#); Rankin *et al.*, [2003](#); Rosen *et al.*, [2002a](#), [2005](#); Williams *et al.*, [2005](#)) and it is certain that there will be considerable advances over the next few years.

Of relevance to the story of bvFTD was the realization a few years ago that a proportion of patients with this clinical label, bvFTD, failed to progress even over many years of follow-up. Such patients typically lacked atrophy on MRI (Davies *et al.*, [2006](#)). Subsequent work showed that these non-progressors or “phenocopy cases,” who were virtually all men, could be identified by their lack of executive (Hornberger *et al.*, [2008](#)) or memory deficits (Hornberger *et al.*, [2010](#)) and preservation of activities of daily living. (Piguet *et al.*, [2011](#)). The etiology of the phenocopy syndrome remains unclear. A proportion of cases may have the *C9orf72* (chromosome 9 open reading frame 72) mutation (discussed below). Others have longstanding personality disorders and decompensate in later life. These findings contributed to the revision of criteria for bvFTD with much more clearly defined symptoms and the need for brain imaging changes, plus evidence of progression, to qualify for a diagnosis of probable, rather than possible, bvFTD (Rascovsky *et al.*, [2011](#)).

Progressive aphasia and semantic dementia

The other strand of the story concerns the rediscovery of the syndrome of progressive aphasia in association with focal left temporal lobe or perisylvian atrophy. In [1982](#) Mesulam reported six patients with a history of insidiously worsening aphasia in the absence of signs of more generalized cognitive failure. One of these patients underwent a brain biopsy, which revealed non-specific histology without specific markers of either Alzheimer's or Pick's disease. Following Mesulam's seminal paper, approximately 100 patients with so-called PPA were reported over the next decade (for reviews, see Hodges and Patterson, [1996](#); Mesulam and Weintraub, [1992](#); Snowden *et al.*, [1996a](#)). It became gradually clear that, although the term PPA was being applied to a range of very different cases, within this spectrum there were two identifiable and distinct aphasic syndromes: progressive non-fluent aphasia (PNFA) and semantic dementia (SD), sometimes referred to as progressive fluent aphasia. In the former syndrome, speech is halting and distorted with frank articulatory and syntactic errors. Comprehension mirrors output in that single-word (semantic) comprehension is relatively intact but patients have difficulty understanding syntactically complex sentences. Oro-buccal apraxia commonly accompanies the language disorder. In the latter syndrome, speech remains fluent and well-articulated but becomes progressively devoid of content words. The language and other non-verbal cognitive deficits observed in these fluent-aphasic patients reflect a breakdown in semantic memory, which has led many authors to apply the label of “semantic dementia” first coined by Snowden *et al.*, in 1989 (Hodges and Patterson, [1996](#); Hodges *et al.*, [1992](#), [1994](#); Snowden *et al.*, [1989](#)).

Although the term “semantic dementia” (SD) is recent, the syndrome has been recognized under different labels for many years. As emphasized

above, Pick ([1892](#), [1904](#)) and a number of other early authors (Mingazzini, [1913](#); Rosenfeld, [1909](#); Schneider, [1927](#); Stertz, [1926](#)) recognized the outstanding clinical manifestation of temporal lobe atrophy as “amnesic aphasia” or “transcortical sensory aphasia,” together with a type of dementia variously described as a reduction in categorical or abstract thinking, psychic blindness, or associative agnosia (Malamud and Boyd, [1940](#); Mingazzini, [1913](#); Robertson *et al.*, [1958](#)). These features – amnesic aphasia and associative agnosia – were united under the rubric of degraded semantic memory by Warrington ([1975](#)) who reported three patients. Drawing on the work of Tulving ([1972](#), [1983](#)), Warrington recognized that the progressive anomia in her patients was not simply a linguistic deficit, but reflected a fundamental loss of semantic memory (or knowledge) about objects and concepts which thereby affected naming, word comprehension, and object recognition. Semantic memory is the term applied to the component of long-term memory that represents our knowledge about things in the world and their inter-relationships, facts and concepts, as well as words and their meaning (Garrard *et al.*, [1997](#); Hodges and Patterson, [1997](#); Hodges *et al.*, [1992](#), [1998](#)). Cases of SD have also been recognized for many years in Japan as cases of “Gogi (word meaning) aphasia” (Imura *et al.*, [1971](#); Morita *et al.*, [1987](#); Sasanuma and Mondì, [1975](#); Tanabe, [1992](#); Tanabe *et al.*, [1992](#)). The syndrome of SD has been particularly important from a theoretical perspective because, in contrast to Alzheimer's disease, patients have relatively good day-to-day (episodic) memory and autobiographical memory, intact immediate or working memory (at least as assessed by digit span), and good visually based problem-solving and visuoperceptual abilities (Graham and Hodges, [1997](#); Hodges and Graham, [1998](#); Hodges *et al.*, [1995](#), [1999](#), [2010](#); Patterson and Hodges, [2000](#)). This relative selectivity of the semantic memory impairment in SD makes these patients ideal subjects for the study of the effects of semantic dissolution

uncontaminated by other cognitive deficits. As discussed elsewhere, however, the situation is somewhat more complex than when it first appeared both in terms of the purity of the syndrome and the insights afforded into the interaction between semantic memory and other putative “cognitive modules.”

The above description is, of course, an oversimplification and gives the impression that cases can be neatly divided into PNFA and SD. In practice things are much less straightforward. First of all, some authors have claimed that there is a coherent third progressive aphasic syndrome (logopenic PA), characterized by word-finding difficulty and anomia but without significant comprehension impairment, and reduced verbal span, which is associated with posterior temporal, inferior parietal, or angular gyrus pathology (Gorno-Tempini *et al.*, [2004](#); Sonty *et al.*, [2003](#)), with the suggestion that such cases have underlying Alzheimer's disease pathology. In a recent study using Pittsburgh compound B (PiB) as a marker of Alzheimer's pathology we were able to confirm the presence of this third logopenic variant in association with increased PiB retention (Leyton *et al.*, [2011](#)). Other authors have claimed that patients who fall in the middle ground between SD and PNFA have no clear defining features (Sajjadi *et al.*, [2012](#)). The identification of this third variant was one of the major factors underlying the revision of criteria for the three subtypes of PPA (Gorno-Tempini *et al.*, [2011](#)). Investigation of these logopenic cases is a topic of considerable current interest.

Second, although this does not affect the issue of the classification of two language variants of FTD, many patients with features of SD also have prominent behavioral changes, and semantic deficits can be seen in patients with bvFTD. Indeed in our clinics we have often seen patients with a mixture of these two syndromes. Finally, there is the problem of how to categorize cases that have all of the classic features of PNFA or SD but have

additional “exclusion” features, such as subtle, but definite, visuospatial defects, poor episodic memory, or apraxia.

Our paper in 1992 (Hodges *et al.*, [1992](#)) defined the core cognitive aspects of SD and drew attention to the association between this cognitive profile and the relatively circumscribed and asymmetric left > right temporal lobe atrophy that has subsequently been confirmed and refined in a number of publications (Davies *et al.*, [2004](#); Galton *et al.*, [2001](#); Mummery *et al.*, [1999](#)). This typical left > right pattern raises the issue of the cognitive and/or behavioral signatures of the less common pattern of relatively isolated right, or right > left, temporal atrophy. Although we almost certainly encountered earlier patients with the syndrome now associated with prominent right temporal atrophy, the first clearly documented patient (VH) was reported as a case of gradually progressive prosopagnosia (Evans *et al.*, [1995](#)): VH was unable to identify from face or name even very famous people (e.g., Margaret Thatcher) yet had relatively intact general semantic and autobiographical memory (Kitchener and Hodges, [1999](#)). Over the past few years a number of authors have reported such cases, confirming the role of the right temporal lobe in the representation of knowledge about people (Gainotti *et al.*, [2003](#); Gentileschi *et al.*, [1999](#), [2001](#); Thompson *et al.*, [2003](#)). In parallel with this literature, the group led by Bruce Miller drew attention to the bizarre behaviors (including irritability, impulsiveness, alterations in dress, limited and fixed ideas, and decreased facial expression) exhibited by patients with predominantly right temporal lobe atrophy (Edwards Lee *et al.*, [1997](#); Miller *et al.*, [1997](#)). A study in 2003, drawing on our experience of 80 cases of whom a quarter had right-predominant atrophy, pulled together these observations by demonstrating that the right > left group tended to present with changes in person recognition *and* alterations in personality, while the more common

left > right group had the typical deterioration of semantic memory for words and objects (Thompson *et al.*, [2003](#)).

The adoption of the term semantic variant PPA to replace the label SD (Gorno-Tempini *et al.*, [2011](#)) creates considerable difficulty in categorizing right-SD cases who do not have prominent aphasia.

Frontotemporal dementia and frontotemporal lobar degeneration

The final terms to be considered are FTD and frontotemporal lobar degeneration (FTLD). In 1994 the Lund and Manchester groups introduced the term FTD (Brun *et al.*, [1994](#)) to describe patients with progressive changes in behavior/personality and suggested tentative criteria for the diagnosis. Then four years later a broad group of experts met and unified FTD with the progressive aphasia (Neary *et al.*, [1998](#)). They proposed the general label FTLD with three subforms: FTD, by which was meant the predominantly behavioral variant with prominent language deficits, and the two aphasic variants, SD and PNFA. Criteria for each syndrome were proposed with major and minor inclusion features and exclusion features. This clearly represented a major advance, but did have the consequence of mixing levels of description in that FTD implies a distinct anatomical locus, whereas SD and PNFA are descriptive clinical syndromes. The use of the label FTD for those with prominent aphasia is perhaps confusing and implies that temporal lobe involvement is an invariable accompaniment of the behavioral syndrome. The “criteria” are also more akin to clinical guidelines since it is not clear how many features need to be present and whether the exclusion features are absolute. For instance, severe amnesia is said to be an exclusion feature, but it is now clear that a fairly high proportion of patients with pathologically proven FTD have significant memory impairment and in some this is of the severity seen in Alzheimer's

disease (Graham *et al.*, [2005](#)). A number of retrospective clinicopathologic studies have examined the utility of the FTLD criteria (Hodges *et al.*, [2004](#); Josephs *et al.*, [2006](#); Rosen *et al.*, [2002b](#)).

In Cambridge we adopted a hybrid classification. The term FTD is preferred as the superordinate label applied to the whole group with a subdivision into two main variants (bvFTD and PPA). A very similar classification was proposed by Grossman ([2002](#)) who used the terms behavioral disorder and dysexecutive syndrome instead of bvFTD. An all-American group led by Guy McKhann ([2001](#)), the originator of the famous NINCDS–ADRDA criteria for Alzheimer's disease (McKhann *et al.*, [1984](#)), have also proposed clinical criteria for FTD with a dichotomy between a behavioral presentation and a language presentation. This has the benefit of simplicity but conflates PNFA and SD. These criteria have not stood the test of time and have been replaced by two influential international groups with proposals for criteria to diagnose bvFTD (Rascovsky *et al.*, [2011](#)) and for three variants of PPA (Gorno-Tempini *et al.*, [2011](#)).

One might wish to ask why these quite distinct syndromes should be regarded as variants of a single disorder in the first place. In answer to this question, three lines of evidence can be examined: (1) the degree of clinical overlap, (2) radiologic overlap, and (3) the spectrum of underlying pathology.

Clinically, patients often present with features of two (or even all three) of these seemingly distinct syndromes and, over time, the overlap typically increases. Patients with “pure” SD typically develop behavior changes, and in many bvFTD patients, aphasic features become evident on follow-up. The overlap has been emphasized by Andrew Kertesz and his colleagues from London, Ontario who have proposed the general label *Pick's complex* (Kertesz and Munoz, [2003](#); Kertesz *et al.*, [2005](#)). In my experience the overlap between bvFTD and SD in terms of behavioral

changes is particularly striking, whereas such changes seem less of a feature of PNFA. Indeed recent evidence has suggested that there is greater overlap between PNFA and corticobasal syndrome (CBS) at both a clinical and pathologic level (Graham *et al.*, [2003a](#), [2003b](#); Mathew *et al.*, [2012](#)).

The second area of overlap is radiological. Although patients with bvFTD have predominantly frontal atrophy, anterior temporal involvement is common, while those with SD may have accompanying frontal atrophy, again pointing to a clinicopathologic continuation rather than distinctive syndromes (Mummery *et al.*, [2000](#); Rosen *et al.*, [2002a](#)).

Neuropathology remains the gold standard of classification in neurodegenerative disease. Progress in this field has been rapid and is reviewed in detail in [Chapter 13](#). Here I provide a brief overview highlighting some of the landmark discoveries.

The neuropathology of FTD is far more complex than that of Alzheimer's disease. Whereas patients with clinically diagnosed Alzheimer's disease, whether young or old, familial or sporadic, will have pathologically identical changes (intraneuronal tangles and extracellular amyloid plaques), the changes in FTD are heterogeneous.

What are the current facts? The majority, but not all, of patients with one of the FTD syndromes described above have non-Alzheimer's pathology. Although tau-positive inclusions (Pick bodies) were the first form of pathologic change identified in the context of FTD, these constitute a minority of cases. The more recently described transactive response DNA-binding protein 43 (TDP-43) inclusions are the most common histopathologic variant.

If this book had been written a decade ago the section on neuropathology would have stated that a minority of cases have Pick body-positive FTD while the majority have neuronal loss and gliosis, but without distinctive histopathology. The recent and ever-expanding development of

more sophisticated immunohistologic staining techniques has led to the identification of an even wider range of histologic abnormalities in cases of non-Alzheimer dementia involving the frontotemporal cortex (for review see Davies *et al.*, [2005](#); Forman *et al.*, [2006](#); Hodges *et al.*, [2004](#); Jackson and Lowe, [1996](#); Josephs *et al.*, [2011](#); Knopman *et al.*, [2005](#); Mott *et al.*, [2005](#); Rademakers *et al.*, [2013](#)). Three major patterns are currently recognized.

(1) Tau-positive inclusion pathology. This, in turn, encompasses a number of subforms: cases with classic intraneuronal tau-positive Pick bodies, most of whom are sporadic; patients with familial, so-called FTDP-17, pathology who typically display diffuse neuronal and glial tau-positive inclusions without discrete Pick bodies; corticobasal degeneration (CBD) which is characterized by tau-positive pathology with ballooned achromatic neurons and astrocytic plaques; and finally argyrophilic grain disease in which the tau staining is punctate and “grain”-like particularly involving the medial temporal lobe.

(2) TDP-43 pathology. In 2006, TDP-43 was identified in both FTD and motor neuron disease (MND; amyotrophic lateral sclerosis [ALS]) (Neumann *et al.*, [2006](#)). Such pathology is found in patients with mutation of the progranulin (*GRN*) gene and with the expansion of the hexanucleotide repeat in gene *C9orf72* as well as in sporadic cases of FTD and MND. Various subforms of TDP-43 are identified.

(3) FUS or fused in sarcoma pathology. These constitute a minority of cases who are non-familial with young onset, prominent behavioral changes, and caudate atrophy.

A major topic, addressed more fully elsewhere, is the predictability of pathology in vivo. In brief, patients with PNFA typically have tau-positive

pathology although a substantial minority have Alzheimer's with atypical distribution (Chare *et al.*, [2014](#); Knibb *et al.*, [2006](#)). Those with clinical MND have TDP-43-positive inclusion pathology. SD is also typically associated with TDP-43-positive disease but only a minority develops clinical MND (Chare *et al.*, [2014](#); Davies *et al.*, [2005](#)). The pathologic substrate of the commonest form, bvFTD, remains the least predictable. In the combined Sydney–Cambridge series of 61 cases, 26 presented with bvFTD and there were approximately equal numbers with tau-positive and tau-negative pathology (Hodges *et al.*, [2004](#)), subsequently confirmed in a larger study involving a total of 178 cases (Chare *et al.*, [2014](#)).

Familial chromosome 17-linked frontotemporal dementia and the discovery of unique tau pathology

As described in more detail in [Chapter 14](#), linkage was established in a number of families in which FTD is inherited as an autosomal dominant trait to the region of chromosome 17 (q21–22) containing the gene for the microtubule-associated protein tau (Wilhelmsen, [1997](#)). The story of the chromosome 17 linkage is extraordinary in a number of ways. Families around the world with what has become known as FTD with parkinsonism linked to chromosome 17 or FTDP-17 (Spillantini *et al.*, [1998a](#)) had originally been reported under a range of headings including: disinhibition–dementia–parkinsonism–amyotrophy complex (Wilhelmsen *et al.*, [1994](#)), rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration (Wszolek *et al.*, [1992](#)), familial progressive subclinical gliosis (Petersen *et al.*, [1995](#)), hereditary dysphasia and dementia (Morris *et al.*, [1984](#)), hereditary frontotemporal dementia

(Heutink *et al.*, [1997](#)), familial multiple system tauopathy with presenile dementia (Spillantini *et al.*, [1997](#)), familial presenile dementia with psychosis (Sumi *et al.*, 1992), and Pick's disease (Schenk, [1951](#)). In 1996 a meeting of representatives from all of the groups identifying linkage to chromosome 17 was held in Ann Arbor, Michigan (Foster *et al.*, [1997](#)). Comparison of clinical and pathologic data revealed a great deal of similarity between the families who all shared the characteristics of predominantly frontotemporal distribution of pathology with marked behavioral changes. Extrapyrimal dysfunction was present in most. In some families psychotic symptoms were a major feature and a number had amyotrophy. It was recognized at that time that some of the families shared the common pathology with microtubule-associated protein tau-positive inclusions. Progress in the field was then rapid. It was soon discovered that most, if not all, families had diffuse neuronal and glial tau inclusions with a distinctive morphologic pattern, leading to the coining of the term “familial tauopathy” and the suggestion that the disease might reflect a mutation in the gene for tau protein known to be located in the 17q21–22 region (Spillantini *et al.*, [1998a](#)). Within two years of the Ann Arbor meeting, several groups had identified the genetic mutation which, as predicted, was in the gene for tau protein (Dumanchin *et al.*, [1998](#); Hutton *et al.*, [1998](#); Poorkaj *et al.*, [1998](#); Spillantini *et al.*, [1998b](#)).

Since 1998, more than 30 different mutations of the gene for tau protein have been identified, largely involving the coding regions, particularly the so-called microtubule-binding domains (exons 9–12) of the gene for tau. There has been an explosion of interest in the molecular pathology of tau. Although the histopathologic appearances in cases with mutations of the gene for tau are consistent, the clinical phenotypes across and even within families have varied considerably, suggesting that other factors influence the

distribution of pathologic changes within the brain. It is also clear that much remains to be learnt.

Very recently, interest has shifted to cases with ubiquitin-positive pathology, particularly the growing number of familial cases which have all been linked to chromosome 17 (Mackenzie *et al.*, [2006](#); Van der Zee *et al.*, [2006](#)). Just as the first edition of this book was nearing completion, two groups reported mutations in the gene encoding progranulin, close to but apparently independently of the microtubule-associated protein tau (*MAPT*) gene (Baker *et al.*, [2006](#); Cruts *et al.*, [2006](#)). Moreover, it seems that progranulin mutations are relatively common as over 30 families were discovered within months of the original discovery. Another recent genetic breakthrough involves the well-known Danish kindred from Jutland. Linkage to chromosome 3 was established in 1993 (Brown *et al.*, [1993](#)) but in 2005 a mutation in the endosomal sorting complex required for transport III (ESCRT-III) complex subunit *CHMP2B* gene was described in affected members of the family and in one unrelated sporadic Cambridge patient (Skibinski *et al.*, [2005](#)). A recent large-scale screen of 141 familial probands from the USA and UK suggests that in contrast to *MAPT* and progranulin this mutation is extremely rare (Cannon *et al.*, [2006](#)).

The even more recent discovery of the *C9orf72* gene expansion is best considered after discussing the overlap between FTD and MND.

Frontotemporal dementia with motor neuron disease

Although MND has traditionally been regarded as a disorder which spares higher cognitive abilities, it has become clear since early reports from Japan (Mitsuyama and Takamiya, [1979](#)) that the rate of dementia in MND is

significantly greater than expected, and conversely a significant minority of patients with FTD develop features of MND (for reviews see Bak and Hodges, [1999](#); Burrell *et al.*, [2011](#); Caselli *et al.*, [1993](#); Lillo *et al.*, [2010](#), [2011](#); Neary *et al.*, [1990](#); Rakowicz and Hodges, [1998](#)). Many patients with the overlap syndrome present with behavioral changes and/or progressive aphasia, which then progresses rapidly, followed by the emergence of bulbar features and mild limb amyotrophy, although the reverse sequence can be seen. Such patients were noted to have prominent neuropsychiatric features including psychosis (Lillo and Hodges, [2010](#)), which is interesting in the context of the *C9orf72* mutation cases.

There is also evidence that patients with the MND-dementia/aphasia complex have disproportionate impairment of verb, compared with noun, knowledge (Bak and Hodges, [1997](#); Bak *et al.*, [2001](#)), which is pertinent to the hypothesis that some components of the widespread semantic network in the brain are located in or near corresponding sensory/motor areas.

The topic of the degree of overlap between MND and FTD has become one of active investigation. Our studies have suggested that subtle behavioral changes, particularly apathy, are very common in MND and often precede classic motor symptoms (Lillo *et al.*, [2011](#); Mioshi *et al.*, [2014](#)), and that such symptoms impact significantly on caregiver burden (Lillo *et al.*, [2012](#)). Viewed from the opposite perspective, it appears that perhaps 10–20% of patients with FTD will develop frank MND although a much higher proportion show subtle signs of motor neuron dysfunction; however, the long-term implications of the latter finding remains unclear (Burrell *et al.*, [2011](#)). [Chapter 6](#) provides more detail on this dimension of overlap within the FTD spectrum.

Discovery of the *C9orf72* mutation

The latest piece of the genetics puzzle links FTD to MND. It had been clear that certain families included members suffering from both of these disorders and that the responsible gene was *C9orf72*. In 2011 an exciting discovery was the expansion of a hexanucleotide repeat in the gene *C9orf72*, soon established to be the commonest genetic cause of both FTD and MND (DeJesus-Hernandez *et al.*, [2011](#); Renton *et al.*, [2011](#)). As well as accounting for a high proportion of familial cases, this mutation appears to be a relatively common cause of cases (perhaps around 5–10%) of apparently sporadic bvFTD (Hodges, [2012](#)). From a clinical perspective, such cases appear atypical in that they may have a slowly progressive or indolent course with prominent psychiatric features and relatively little in the way of brain atrophy (Devenney *et al.*, [2014](#)). These findings beg the question of how many cases with the non-progressive or phenocopy syndrome may turn out to have this expansion.

Corticobasal syndrome

The other clinical syndrome which overlaps considerably with FTD is CBS, originally described as a movement disorder characterized by an asymmetric akinetic-rigid syndrome with prominent apraxia culminating, in some instances, in the striking feature of alien or anarchic hand (Gibb *et al.*, [1989](#)) and associated with a characteristic pattern of tau-positive neuropathology involving basal ganglia and parietal and frontal cortices (Dickson *et al.*, [2002](#); Feany and Dickson, [1996](#)). It is now clear that cognitive deficits are virtually universal in CBS (Graham *et al.*, [2003a](#), [2003b](#)). The pattern of dementia fits most closely with PNFA, although frontal-executive deficits are also common (Graham *et al.*, [2003a](#)). One relatively unique feature is the prominence of visuospatial and perceptual

deficits not seen in other forms of FTD (Bak *et al.*, [2005](#), [2006](#)). Another facet of the overlap is that the typical tau-positive CBD neuropathology may be found in patients presenting with FTD syndromes without motor features, at least in the earlier stages of their illness (Mathuranath *et al.*, [2000](#)). To add further to the confusion, it is emerging that some patients with an in vivo diagnosis of CBS may have Alzheimer's disease neuropathology at autopsy (Boeve *et al.*, [1999](#); Doran *et al.*, [2003](#); Schneider *et al.*, [1997](#); Shelley *et al.*, [2009](#)). It remains unclear whether such patients can be distinguished in life from those without Alzheimer's pathology (Alexander *et al.* [2014](#); Burrell *et al.*, [2013](#)). Further details on this domain of overlap within the FTD spectrum can be found in [Chapter 7](#).

Conclusions

It should be clear from this overview that research on FTD is flourishing and that the knowledge base is expanding rapidly. Searching PubMed under the terms FTD, FTLD, or Pick's reveals a little over 4000 papers, half of which have been published since the year 2010. Many of the recent papers concern aspects of molecular pathology and genetics but, compared with Alzheimer's disease, a very high proportion of the papers still deal with the neuropsychology of FTD. One of the remarkable facts about the disorder, which makes it so interesting to study from the perspective of behavioral neurology, is the involvement of brain systems involved in social cognition, language, and semantic memory which can be strikingly selective for a number of years. The following chapters now flesh out this outline and review the current status from many different viewpoints.

References

Alexander SK, Rittman T, Xuereb JH *et al.* 2014. Validation of the new consensus criteria for the diagnosis of Corticobasal Degeneration. *Journal of Neurology, Neurosurgery, and Psychiatry* **85**:925–9.

Alzheimer A. 1911. Über eigenartige Krankheitsfalle des späteren Alters. *Zeitschrift für die und Gesellschaft für Neurologie und Psychiatrie* **4**:356–85.

Bak T, Hodges JR. 1997. Noun-verb dissociation in three patients with motor neurone disease and aphasia. *Brain and Language* **60**:38–40.

Bak T, Hodges JR. 1999. Cognition, language and behaviour in motor neurone disease: evidence of frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders* **10**:29–32.

Bak TH, O'Donovan DG, Xuereb JH, Boniface S, Hodges J. 2001. Selective impairment of verb processing associated with pathological changes in the Brodmann areas 44 and 45 in the motor neurone disease/dementia/aphasia syndrome. *Brain* **124**:103–20.

Bak TH, Crawford LM, Hearn VC, Mathuranath PS, Hodges JR. 2005. Subcortical dementia revisited: similarities and differences in cognitive function between progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). *Neurocase* **11**:268–73.

Bak T, Caine D, Hearn VC, Hodges JR. 2006. Visuospatial functions in atypical parkinsonian syndromes. *Journal of Neurology, Neurosurgery, and Psychiatry* **77**:454–6.

Baker M, Mackenzie IR, Pickering-Brown SM *et al.* 2006. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* **24**:916–19.

Bertoux M, Volle E, Funkiewiez A *et al.* 2012. Social Cognition and Emotional Assessment (SEA) is a marker of medial and orbital frontal functions: a voxel-

based morphometry study in behavioral variant of frontotemporal degeneration. *Journal of the International Neuropsychological Society* **18**:972–85.

Boeve BF, Maraganore DM, Parisi JE *et al.* 1999. Pathological heterogeneity in clinically diagnosed corticobasal degeneration. *Neurology* **53**:795–800.

Bozeat S, Gregory CA, Lambon Ralph MA, Hodges JR. 2000. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of Neurology, Neurosurgery, and Psychiatry* **69**:178–86.

Brown J, Gydesen S, Sorensen SA *et al.* 1993. Genetic characterization of a familial non-specific dementia originating in Jutland, Denmark. *Journal of Neurological Sciences* **114**:138–43.

Brun A. 1987. Frontal lobe degeneration of non-Alzheimer's type. I. Neuropathology. *Archives of Gerontology and Geriatrics* **6**:209–33.

Brun A, Englund B, Gustafson L *et al.* 1994. Clinical and neuropathological criteria for frontotemporal dementia. The Lund Manchester Groups. *Journal of Neurology, Neurosurgery, and Psychiatry* **57**:416–18.

Burrell J, Kiernan MC, Vucic S, Hodges JR. 2011. Motor neuron dysfunction in frontotemporal dementia. *Brain* **134**(Pt 9):2582–94.

Burrell J, Hornberger M, Villemagne V, Rowe C, Hodges JR. 2013. Clinical profile of PiB-positive corticobasal syndrome. *PLoS One* **8**(4):e61025.

Cannon A, Baker M, Boeve BF *et al.* 2006. CHMP2B mutations are not a common cause of frontotemporal lobar degeneration. *Neuroscience Letters* **398**:83–4.

Caselli RJ, Windebank AJ, Petersen RC *et al.* 1993. Rapidly progressive aphasic dementia and motor neuron disease. *Annals of Neurology* **33**:200–7.

Chare L, Hodges JR, Leyton CE *et al.* 2014. New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications. *Journal of Neurology, Neurosurgery, and Psychiatry* **85**(8):865–70.

Cruts M, Gijselinck I, Van der Zee J *et al.* 2006. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature* **442**:920–4.

Cummings JL, Mega M, Gray K *et al.* 1994. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **44**:2308–14.

Davies RR, Graham KS, Xuereb JH, Williams GB, Hodges JR. 2004. The human perirhinal cortex and semantic memory. *European Journal of Neuroscience* **20**:2441–6.

Davies RR, Hodges JR, Kril J *et al.* 2005. The pathological basis of semantic dementia. *Brain* **128**:1984–5.

Davies RR, Kipps CM, Mitchell J *et al.* 2006. Progression in frontotemporal dementia: identifying a benign behavioral variant by MRI. *Archives of Neurology* **63**: 1627–31.

DeJesus-Hernandez M, Mackenzie IR, Boeve BF *et al.* 2011. Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* **72**(2):245–56.

Devenney E, Hornberger M, Irish M *et al.* 2014. Frontotemporal dementia associated with the C9ORF72 mutation: a unique clinical profile. *JAMA Neurology* **71**(3):331–9.

Dickson DW, Bergeron C, Chin SS *et al.* 2002. Neuropathologic criteria for corticobasal degeneration. *Journal of Neuropathology and Experimental Neurology* **61**:935–46.

Doran M, du Plessis DG, Enevoldson TP *et al.* 2003. Pathological heterogeneity of clinically diagnosed corticobasal degeneration. *Journal of Neurological Science* **216**:127–34.

Dumanchin C, Camuzat A, Campion D *et al.* 1998. Segregation of a missense mutation in the microtubule-associated protein tau gene with familial frontotemporal dementia and parkinsonism. *Human Molecular Genetics* **7**:1825–9.

Edwards Lee T, Miller B, Benson F *et al.* 1997. The temporal variant of frontotemporal dementia. *Brain* **120**:1027–40.

Evans JJ, Heggs AJ, Antoun N, Hodges JR. 1995. Progressive prosopagnosia associated with selective right temporal lobe atrophy: a new syndrome? *Brain* **118**:1–13.

Feany MB, Dickson DW. 1996. Neurodegenerative disorders with extensive tau pathology: a comparative study and review. *Annals of Neurology* **40**:139–48.

Ferraro A, Jervis GA. 1940. Clinicopathologic study of a case of Pick's disease. *Psychiatric Quarterly (New York NY)* **17**:17–29.

Forman MS, Farmer J, Johnson JK *et al.* 2006. Frontotemporal dementia: clinicopathological correlations. *Annals of Neurology* **59**:952–62.

Foster NL, Wilhelmsen K, Sima AAF *et al.* 1997. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. *Annals of Neurology* **41**:706–15.

Gainotti G, Barber A, Marra C. 2003. Slowly progressive defect in recognition of familiar people in a patient with right anterior temporal atrophy. *Brain* **126**:792–803.

Galton CJ, Patterson K, Graham KS *et al.* 2001. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* **57**:216–25.

Garrard P, Perry R, Hodges JR. 1997. Disorders of semantic memory. *Journal of Neurology, Neurosurgery, and Psychiatry* **62**:431–5.

Gentileschi V, Sperber S, Spinnler H. 1999. Progressive defective recognition of familiar people. *Neurocase* **5**:407–24.

Gentileschi V, Sperber S, Spinnler H. 2001. Crossmodal agnosia for familiar people as a consequence of right infero polar temporal atrophy. *Cognitive Neuropsychology* **18**:439–63.

Gibb WRG, Luthert PJ, Marsden CD. 1989. Corticobasal degeneration. *Brain* **112**:1171–92.

Girling DM, Berrios GE. 1994. On the relationship between senile cerebral atrophy and aphasia (translation of Pick A. 1892. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prager Medicinische Wochenschrift* 17:165–7). *History of Psychiatry* **5**:542–7.

Girling DM, Berrios GE. 1997. On the symptomatology of left-sided temporal lobe atrophy (translation of Pick A. 1904. Zur Symptomatologie der linksseitigen Schäfenlappenatrophie. *Monatschrift für Psychiatrie und Neurologie* 16:378–88). *History of Psychiatry* **8**:149–59.

Gorno-Tempini M, Dronkers N, Rankin K *et al.* 2004. Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology* **55**:335–46.

Gorno-Tempini ML, Hillis AE, Weintraub S *et al.* 2011. Classification of primary progressive aphasia and its variants. *Neurology* **76**(11):1006–14.

Graham AJ, Davies R, Xuereb J *et al.* 2005. Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* **128**:597–605.

Graham KS, Hodges JR. 1997. Differentiating the roles of the hippocampal complex and the neocortex in long-term memory storage: evidence from the study of semantic dementia and Alzheimer's disease. *Neuropsychology*

11:77–89.

Graham NL, Bak T, Hodges JR. 2003a. Corticobasal degeneration as a cognitive disorder. *Movement Disorders* **18**:1224–32.

Graham NL, Patterson K, Bak T, Hodges JR. 2003b. Language function and dysfunction in corticobasal degeneration. *Neurology* **61**:493–9.

Gregory CA, Lough S, Stone VA *et al.* 2002. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain* **125**:752–64.

Grossman M. 2002. Frontotemporal dementia: a review. *Journal of the International Neurological Society* **8**:566–83.

Gustafson L. 1987. Frontal lobe degeneration of non-Alzheimer's type II: clinical picture and differential diagnosis. *Archives of Gerontology and Geriatrics* **6**:209–23.

Heutink P, Stevens M, Rizzu P *et al.* 1997. Hereditary frontotemporal dementia is linked to chromosome 17q21-q22: a genetic and clinicopathological study of three Dutch families. *Annals of Neurology* **41**:150–9.

Hodges JR. 2012. Familial frontotemporal dementia and amyotrophic lateral sclerosis associated with the C9ORF72 hexanucleotide repeat. *Brain* **135**(Pt 3):652–5.

Hodges JR, Graham KS. 1998. A reversal of the temporal gradient for famous person knowledge in semantic dementia: implications for the neural organisation of long-term memory. *Neuropsychologia* **36**:803–25.

Hodges JR, Patterson K. 1996. Non-fluent progressive aphasia and semantic dementia: a comparative neuropsychological study. *Journal of the International Neuropsychological Society* **2**:511–24.

Hodges JR, Patterson KE. 1997. Semantic memory disorders. *Trends in Cognitive Science* **1**:67–72.

Hodges JR, Patterson K, Oxbury S, Funnell E. 1992. Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. *Brain* **115**:1783–806.

Hodges JR, Patterson K, Tyler LK. 1994. Loss of semantic memory: implications for the modularity of mind. *Cognitive Neuropsychology* **11**:505–42.

Hodges JR, Graham N, Patterson K. 1995. Charting the progression in semantic dementia: implications for the organisation of semantic memory. *Memory* **3**:463–95.

Hodges JR, Garrard P, Patterson K. 1998. Semantic dementia. In Kertesz A, Munoz DG, eds. *Pick's Disease and Pick Complex* pp. 83–104. New York: Wiley-Liss, Inc.

Hodges JR, Patterson K, Ward R *et al.* 1999. The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology* **13**:31–40.

Hodges JR, Davies R, Xuereb J *et al.* 2004. Clinicopathological correlates in frontotemporal dementia. *Annals of Neurology* **56**:399–406.

Hodges JR, Mitchell J, Dawson K *et al.* 2010. Semantic dementia: demography, familial factors and survival in a consecutive series of 100 cases. *Brain* **133**(Pt 1):300–6.

Hornberger M, Piguet O, Kipps CM, Hodges JR. 2008. Executive function in progressive and non-progressive behavioural variant frontotemporal dementia. *Neurology* **71**(19):1481–8.

Hornberger M, Piguet O, Graham A, Nestor PJ, Hodges JR. 2010. How preserved is episodic memory in behavioral variant frontotemporal dementia?

Neurology **74**:472–9.

Hornberger M, Geng J, Hodges JR. 2011. Convergent evidence of orbitofrontal cortex grey and white matter changes related to disinhibition in behavioural variant frontotemporal dementia. *Brain* **134**(Pt 9):2502–12.

Hutton M, Lendon CL, Rizzu P *et al.* 1998. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **393**:702–5.

Imura T, Nogami Y, Asakawa K. 1971. Aphasia in Japanese language. *Nihon University Journal of Medicine* **13**:69–90.

Jackson M, Lowe J. 1996. The new neuropathology of degenerative frontotemporal dementias. *Acta Neuropathologica* **91**:127–34.

Josephs KA, Petersen RC, Knopman DS *et al.* 2006. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. *Neurology* **66**:41–8.

Josephs KA, Hodges JR, Snowden JS *et al.* 2011. Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathologica* **122**(2):137–53.

Kamo H, McGeer PL, Harrop R *et al.* 1987. Positron emission tomography and histopathology in Pick's disease. *Neurology* **37**:439–45.

Katzman R. 1986. Differential diagnosis of dementing illness. *Neurologic Clinic of North America* **4**:329–40.

Keane J, Calder AJ, Hodges JR, Young AW. 2002. Face and emotion processing in frontal variant frontotemporal dementia. *Neuropsychologia* **40**:655–65.

Kertesz A, Munoz DG. 1998. *Pick's Disease and Pick Complex*. New York: Wiley-Liss, Inc.

Kertesz A, Munoz DG. 2003. Primary progressive aphasia and Pick complex.

Journal of Neurologic Sciences **206**:97–107.

Kertesz A, Nadkarni N, Davidson W, Thomas AW. 2000. The frontal behavioral inventory in the differential diagnosis of frontotemporal dementia. *Journal of the International Neuropsychological Society* **6**:460–8.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. 2005. The evolution and pathology of frontotemporal dementia. *Brain* **128**:1996–2005.

Kitchener E, Hodges JR. 1999. Impaired knowledge of famous people and events and intact autobiographical knowledge in a case of progressive right temporal lobe degeneration: implications for the organization of remote memory. *Cognitive Neuropsychology* **16**:589–607.

Kloeters S, Bertoux M, O'Callaghan C, Hodges JR, Hornberger M. 2013. Money for nothing – Atrophy correlates of gambling decision making in behavioural variant frontotemporal dementia and Alzheimer's disease. *NeuroImage: Clinical* **2**:263–72.

Knibb JA, Xuereb JH, Patterson K, Hodges JR. 2006. Clinical and pathological characterisation of progressive aphasia. *Annals of Neurology* **59**:156–65.

Knopman DS, Mastri AR, Frey WH, Sung JH, Rustan T. 1990. Dementia lacking distinctive histological features: a common non-Alzheimer degenerative disease. *Neurology* **40**:251–6.

Knopman DS, Boeve, BF, Parisi JE *et al.* 2005. Antemortem diagnosis of frontotemporal lobar degeneration. *Annals of Neurology* **57**:480–8.

Kumfor F, Piguet O. 2012. Disturbance of emotion processing in frontotemporal dementia: a synthesis of cognitive and neuroimaging findings. *Neuropsychology Review* **22**(3):280–97.

Kumfor F, Irish M, Hodges J, Piguet O. 2013. Discrete neural correlates for the recognition of basic emotions in frontotemporal dementia. *PLoS One*

8(6):e67457.

Leyton CE, Villemagne VL, Savage S *et al.* 2011. Subtypes of progressive aphasia: application of the International Consensus Criteria and validation using β -amyloid imaging. *Brain* **134**(Pt 10):3030–43.

Lillo P, Hodges JR. 2010. Cognition and behaviour in motor neurone disease (MND). *Current Opinion in Neurology* **23**(6):638–42.

Lillo P, Garcin B, Bak T, Hornberger M, Hodges J. 2010. Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis. *Archives of Neurology* **67**(7):826–30.

Lillo P, Mioshi E, Zoing M, Kiernan M, Hodges JR. 2011. How common are behavioral changes in amyotrophic lateral sclerosis? *Amyotrophic Lateral Sclerosis* **12**(1):45–51.

Lillo P, Mioshi E, Hodges JR. 2012. Caregiver burden in amyotrophic lateral sclerosis is more dependent on patients' behavioral changes than physical disability: a comparative study. *BMC Neurology* **12**:156.

Lough S, Kipps CM, Treise C *et al.* 2006. Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia* **44**:950–8.

Löwenberg K, Arbor A. 1936. Pick's disease: a clinicopathologic contribution. *Archives of Neurology and Psychiatry* **36**:768–89.

Löwenberg K, Boyd DA, Salon DD, Arbor A. 1939. Occurrence of Pick's disease in early adult years. *Archives of Neurology and Psychiatry* **41**:1004–20.

Mackenzie IR, Baker M, West G *et al.* 2006. A family with tau-negative frontotemporal dementia and neuronal intranuclear inclusions linked to chromosome 17. *Brain* **129**:853–67.

Malamud N, Boyd DA. 1940. Pick's disease with atrophy of the temporal lobes:

a clinicopathologic study. *Archives of Neurology and Psychiatry* **43**:210–22.

Mansvelt JV. 1954. *Pick's Disease: A Syndrome of Lobar Cerebral Atrophy, its Clinico-anatomical and Histopathological Types*. Utrecht: Thesis.

Mathew R, Bak TH, Hodges JR. 2012. Diagnostic criteria for corticobasal syndrome: a comparative study. *Journal of Neurology, Neurosurgery, and Psychiatry* **83**(4):405–10.

Mathuranath PS, Xuereb JH, Bak T, Hodges JR. 2000. Corticobasal ganglionic degeneration and/or frontotemporal dementia? A report of two overlap cases and review of literature. *Journal of Neurology, Neurosurgery, and Psychiatry* **68**:304–12.

McKhann G, Drachman D, Folstein M *et al.* 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**:939–44.

McKhann GM, Albert MS, Grossman M *et al.* 2001. Clinical and pathological diagnosis of frontotemporal dementia: report of the Working Group on Frontotemporal Dementia and Pick's Disease. *Archives of Neurology* **58**:1803–9.

Mesulam M. 1982. Slowly progressive aphasia without generalized dementia. *Annals of Neurology* **11**:592–8.

Mesulam MM, Weintraub S. 1992. Primary progressive aphasia. In Boller F, ed. *Heterogeneity of Alzheimer's Disease* pp. 43–66. Berlin: Springer-Verlag.

Miller BL, Cummings JL, Villanueva-Meyer J *et al.* 1991. Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. *Neurology* **41**:1374–82.

Miller BL, Darby A, Benson F, Cummings JL, Miller MH. 1997. Aggressive, socially disruptive and anti-social behaviour associated with frontotemporal

dementia. *British Journal of Psychiatry* **170**:150–4.

Mingazzini G. 1913. On aphasia due to atrophy of the cerebral convolutions. *Brain* **36**:493–524.

Mioshi M, Caga J, Lillo P *et al.* 2014. Neuropsychiatric changes precede classical motor symptoms in ALS and do not affect survival. *Neurology* **82**(2):149–55.

Mitsuyama Y, Takamiya S. 1979. Presenile dementia with motor neuron disease in Japan. A new entity? *Archives of Neurology* **36**:592–3.

Morita K, Kaiya H, Ikeda T, Namba M. 1987. Presenile dementia combined with amyotrophy: a review of 34 Japanese cases. *Archives of Gerontology and Geriatrics* **6**:263–77.

Morris JC, Cole M, Banker BQ, Wright D. 1984. Hereditary dysphasic dementia and the Pick-Alzheimer spectrum. *Annals of Neurology* **16**:455–66.

Mott RT, Dickson DW, Trojanowski JQ *et al.* 2005. Neuropathologic, biochemical and molecular characterization of the frontotemporal dementias. *Journal of Neuropathology and Experimental Neurology* **64**:420–8.

Mummery CJ, Patterson K, Wise RJS *et al.* 1999. Disrupted temporal lobe connections in semantic dementia. *Brain* **122**:61–73.

Mummery C J, Patterson K, Price CJ *et al.* 2000. A voxel based morphometry study of semantic dementia: the relationship between temporal lobe atrophy and semantic dementia. *Annals of Neurology* **47**:36–45.

Neary D, Snowden JS, Bowen DM *et al.* 1986. Cerebral biopsy in the investigation of presenile dementia due to cerebral atrophy. *Journal of Neurology, Neurosurgery, and Psychiatry* **49**:157–62.

Neary D, Snowdon JS, Mann DMA *et al.* 1990. Frontal lobe dementia and

motor neuron disease. *Journal of Neurology, Neurosurgery, and Psychiatry* **53**:23–32.

Neary D, Snowden JS, Gustafson L *et al.* 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**:1546–54.

Neumann MA. 1949. Pick's disease. *Journal of Neuropathology and Experimental Neurology* **8**:255–82.

Neumann M, Sampathu DM, Kwong LK, *et al.* 2006. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* **314**(5796):130–3.

Nichols IC, Weigner WC. 1938. Pick's disease: a specific type of dementia. *Brain* **3**:237–49.

Onari K, Spatz H. 1926. Anatomische beiträge zur lehre von der pickschen umschriebenen grosshirnindenatrophie (Picksche Krankheit). *Zeitschrift für die Gesamte Neurologie und Psychiatrie* **101**:470–511.

Pasquier F, Lebert F, Scheltens P. 1996. *Frontotemporal Dementia*. The Netherlands: ICG Publications.

Patterson K, Hodges JR. 2000. Semantic dementia: one window on the structure and organisation of semantic memory. In Cermak L, ed. *Revised Handbook of Neuropsychology: Memory and its Disorders* pp. 313–35. Amsterdam: Elsevier Science B.V.

Petersen RB, Tabaton M, Chen SG *et al.* 1995. Familial progressive subcortical gliosis: presence of prions and linkage to chromosome 17. *Neurology* **45**:1062–7.

Pick A. 1892. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prager Medicinische Wochenschrift* **17**:165–7.

Pick A. 1904. Zur symptomatologie der linksseitigen Schlafenlappenatrophie. *Monatsschrift für Psychiatrie und Neurologie* **16**:378–88.

Piguet O, Hornberger M, Mioshi M, Hodges JR. 2011. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging and management. *Lancet Neurology* **10**(2):162–72.

Poorkaj P, Bird TD, Wijsman E *et al.* 1998. Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Annals of Neurology* **43**:815–25.

Rademakers R, Neumann M, Mackenzie IR. 2013. Advances in understanding the molecular basis of frontotemporal dementia. *Nature Review Neurology* **8**(8):423–34.

Rahman S, Sahakian B J, Hodges JR, Rogers RD, Robbins TW. 1999. Specific cognitive deficits in mild frontal variant frontotemporal dementia. *Brain* **122**:1469–93.

Rakowicz Z, Hodges JR. 1998. Dementia and aphasia in motor neurone disease: an under recognised association. *Journal of Neurology, Neurosurgery, and Psychiatry* **65**:881–9.

Rankin KP, Kramer JH, Mychack P, Miller BL. 2003. Double dissociation of social functioning in frontotemporal dementia. *Neurology* **60**:266–71.

Rascovsky K, Hodges JR, Knopman D *et al.* 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**(Pt 9):2456–77.

Renton AE, Majounie E, Waite A *et al.* 2011. Hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* **72**(2):257–68.

Robertson EE, Le Roux A, Brown JH. 1958. The clinical differentiation of Pick's disease. *Journal of Mental Science* **104**:1000–24.

Rosen HJ, Gorno-Tempini ML, Goldman WP *et al.* 2002a. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* **58**:198–208.

Rosen HJ, Hartikainen KM, Jagust W *et al.* 2002b. Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. *Neurology* **58**:1608–15.

Rosen HJ, Allison SC, Schauer GF *et al.* 2005. Neuroanatomical correlates of behavioural disorders in dementia. *Brain* **128**:2612–25.

Rosenfeld M. 1909. Die partielle Gorsshirnatrophie. *Journal für Psychologie und Neurologie* **14**:115–30.

Sajjadi SA, Patterson K, Arnold RJ, Watson PC, Nestor PJ. 2012. Primary progressive aphasia: a tale of two syndromes and the rest. *Neurology* **78**(21):1670–7.

Sanders J, Schenk VWD, van Veen P. 1939. A family with Pick's disease. *Verh kon Nederl Akad Wetensch* **38**:1–124.

Sasanuma S, Mondì H. 1975. The syndrome of Gogi (word meaning) aphasia. *Neurology* **25**:627–32.

Schenk VWS. 1951. Maladie de Pick: etude anatomo-clinique de 8 cas. *Annales Medicopsychologiques* **109**:574–87.

Schneider C. 1927. Über Picksche Krankheit. *Monatschrift für Psychologie und Neurologie* **65**:230–75.

Schneider C. 1929. Weitere Beiträge zur Lehre von der Pickschen Krankheit. *Zeitschrift für die gesamte Neurologie und Psychiatrie* **120**:340–84.

Schneider JA, Watts RL, Gearing M, Brewer RP, Mirra SS. 1997. Corticobasal degeneration: neuropathologic and clinical heterogeneity. *Neurology* **48**:959–69.

Shelley BP, Hodges JR, Kipps CM, Xuereb JH, Bak TH. 2009. Is the pathology of corticobasal syndrome predictable in life? *Movement Disorders* **24**(11):1593–9.

Skibinski G, Parkinson NJ, Brown JM *et al.* 2005. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nature Genetics* **37**:806–8.

Snowden JS, Goulding PJ, Neary D. 1989. Semantic dementia: a form of circumscribed cerebral atrophy. *Behavioural Neurology* **2**:167–82.

Snowden JS, Griffiths HL, Neary D. 1996a. Progressive language disorder associated with frontal lobe degeneration. *Neurocase* **2**:429–40.

Snowden JS, Neary D, Mann D. 1996b. *Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia*. New York: Churchill Livingstone.

Sonty SP, Mesulam MM, Thompson CK *et al.* 2003. Primary progressive aphasia: PPA and the language network. *Annals of Neurology* **53**:35–49.

Spillantini MG, Goedert M, Crowther RA *et al.* 1997. Familial multiple system tauopathy with presenile dementia: a disease with abundant neuronal and glial tau filaments. *Proceedings of the National Academy of Science USA* **94**:4113–18.

Spillantini MG, Bird TD, Ghetti B. 1998a. Frontotemporal dementia and parkinsonism linked to chromosome 17: a new group of tauopathies. *Brain Pathology* **8**:387–402.

Spillantini MG, Murrell JR, Goedert M *et al.* 1998b. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proceedings of the National Academy of Science USA* **95**:7737–41.

Stertz G. 1926. Über die Picksche atrophie. *Zeitschrift für die Gesamte Neurologie und Psychiatrie* **101**:729–47.

Sumi SM, Bird TD, Nochlin D, Raskind MA. 1992. Familial presenile dementia with psychosis associated with cortical neurofibrillary tangles and degeneration of the amygdala. *Neurology* **42**:120–7.

Tanabe H. 1992. Personality of typical Gogi (word meaning) aphasics. *Japanese Journal of Neuropsychology* **8**:34–42.

Tanabe H, Ikeda M, Nakagawa Y *et al.* 1992. Gogi (word meaning) aphasia and semantic memory for words. *Higher Brain Function Research* **12**:153–69.

Thompson SA, Patterson K, Hodges JR. 2003. Left/right asymmetry of atrophy in semantic dementia: behavioural cognitive implications. *Neurology* **61**:1196–1203.

Tissot R, Constantinidis J, Richard J. 1975. *La Maladie de Pick*. Paris: Masson.

Tissot R, Constantinidis J, Richard J. 1985. Pick's disease. In Frederiks JAM, ed. *Handbook of Clinical Neurology: Neurobehavioural Disorders* Vol. **2**, pp. 233–46. Amsterdam: Elsevier Science Publishers.

Torralva T, Hodges J, Clark L *et al.* 2007. The relationship between affective decision making and theory of mind in the frontal variant of frontotemporal dementia. *Neuropsychologia* **45**:342–9.

Tulving E. 1972. Episodic and semantic memory. In Tulving E, Donaldson W, eds. *Organisation of Memory*, pp. 381–403. New York: Academic Press.

Tulving E. 1983. *Elements of Episodic Memory*. New York: Oxford University Press.

Van der Zee J, Rademakers R, Engelborghs S *et al.* 2006. A Belgian ancestral haplotype harbours a highly prevalent mutation for 17q21-linked tau-negative FTLD. *Brain* **129**:841–52.

Warrington EK. 1975. Selective impairment of semantic memory. *Quarterly*

Journal of Experimental Psychology **27**:635–57.

Wilhelmsen KC. 1997. Frontotemporal dementia is on the MAP. *Annals of Neurology* **41**:139–40.

Wilhelmsen KC, Lynch T, Pavlou E, Higgins M, Nygaard TG. 1994. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21–22. *American Journal of Human Genetics* **55**:1159–65.

Williams GB, Nestor PJ, Hodges JR. 2005. The neural correlates of semantic and behavioural deficits in frontotemporal dementia. *NeuroImage* **24**:1042–51.

Wszolek ZK, Pfeiffer RF, Bhatt MH *et al.* 1992. Rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration. *Annals of Neurology* **32**:312–20.

Chapter 2

Overview of frontotemporal dementia and its relationship to other neurodegenerative disorders



Paul McMonagle and Andrew Kertesz

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction to terminology and historical aspects

The combination of progressive aphasia and a behavioral disorder appearing in middle age was first ascribed to frontotemporal atrophy by Arnold Pick in a series of articles in the 1890s and early 1900s [[1](#), [2](#)]. Pick's initial case of a progressive aphasic patient with behavioral disturbances had only gross examination without any microscopic examination, but the clinical description and its relationship to focal atrophy is the basis of the syndrome. Pick also linked several cases with focal

atrophy of the left temporal lobe to a clinical picture of word deafness, similar to what is currently referred to as “semantic dementia” (SD) [3, 4]. Silver staining demonstrated round “Pick bodies,” described by Alois Alzheimer, which became the pathologic hallmark of what would eventually be called Pick's disease (PiD).

With the separation of psychiatry and neurology in the twentieth century, interest in cognitive aspects of neurology diminished, if not in continental Europe then certainly in the English-speaking world. In that context the eponymic term held for 60 years until the Lund and Manchester groups revived the clinical entity in the 1980s in a series of prescient papers, but they renamed the condition dementia of the frontal lobe type [5, 6], arguing that only about a quarter of the cases had Pick bodies. Later the term was changed to frontotemporal dementia (FTD) and again to frontotemporal lobar degeneration (FTLD) [7]. The fractionation continued as the aphasic presentation was described as primary progressive aphasia (PPA) [8], and the extrapyramidal component as progressive supranuclear palsy (PSP) [9] or corticobasal degeneration (CBD) [10].

Most historical series of PiD were based on post-mortem examinations with incomplete characterization of clinical features because of the retrospective nature of the studies. This gave rise to the notion that PiD was difficult to diagnose in vivo and was a condition that could only be diagnosed post-mortem by pathologists. It also became apparent that cases of clinical Pick's with frontal and temporal lobe symptoms may not show the prototypical histology at autopsy. The infrequency of Pick bodies in clinical PiD with frontotemporal atrophy led to the idea that PiD was rare. The first attempt to introduce order to pathologic classification of apparently diverse cases with frontotemporal atrophy was presented by Constantinidis and others in 1974 in proposing a simple histology-based classification (types A, B, and C) [11]. Though focusing on histology they felt “in spite of the

dissimilarities between these forms, considering the absence of sufficient knowledge about pathogenesis, it seems prudent at present to maintain the uniqueness of Pick's entity.”

As also discussed in [Chapter 1](#), terminology in FTD is complex, particularly for those new to the field ([Table 2.1](#)). Current models of classification in FTD exist on several different levels; from clinical syndrome (sometimes influenced by patterns of atrophy on imaging), to broad groupings based on clinicopathologic correlations, to the most recent trend of defining specific molecular pathologic entities informed by genetics. Nosologic controversies are not unique to FTD, and are probably inevitable when a disease can be defined clinically, pathologically, and genetically. Despite that, many in the field recognize a unitary concept of overlapping and merging clinical syndromes, some with tighter clinic pathologic correlations than others. The aphasic, behavioral, extrapyramidal, and motor variants were initially described as separate entities, but over time they were recognized as being different presentations affecting different parts of the brain, but with clinical, pathologic, and biologic convergences. FTD is used as the umbrella term for the clinical entity of Pick's disease but often interchangeably with the behavioral variant as Pick's disease itself becomes limited to just the pathologic entity (PiD). FTLD is increasingly used to denote the pathologic entities with a qualifying suffix such as FTLD-tau for tauopathies, etc. Many would prefer to continue using the eponymic term because of its obvious symmetry to Alzheimer's disease (AD), for the sake of caregivers and patients, who dislike the term dementia, and indeed for historical accuracy. Since FTD is used both for the overall disease and ambiguously for the behavioral presentation, the term “Pick complex” was suggested to encompass all the related entities clinically and pathologically [[12](#)]. Pick complex is a unifying concept of the overlapping clinical syndromes of FTD, PPA, corticobasal degeneration

syndrome (CBDS), PSP syndrome (PSPS), FTD with motor neuron disease (FTD-MND), and the underlying neuropathologic findings, emphasizing commonalities rather than differences. It designates both the pathologic and the clinical overlap, avoids the restriction of pathology and clinical symptomatology to the frontotemporal cortex, and acknowledges the relationship to PiD. The term “frontotemporal degeneration” or “frontotemporal dementia” does not acknowledge the frequent subcortical involvement, parietal pathology, and extrapyramidal symptomatology. It is used for both the behavioral presentation and the whole syndrome, which can be confusing, but is at present the most common term used by investigators.

Table 2.1 Currently used abbreviations and acronyms for clinical syndromes of FTD/Pick complex

Clinical syndromes	Abbreviations
Frontotemporal dementia (umbrella term)	FTD, FTLD
Behavioral variant frontotemporal dementia	bvFTD, fvFTD, FTD
Corticobasal syndrome	CBS, CBDS
Frontotemporal dementia with motor neuron disease	FTD-MND
Logopenic progressive aphasia	LPA, lvPPA
Primary progressive aphasia	PPA
Progressive non-fluent aphasia	PNFA, nfvPPA
Progressive supranuclear palsy	PSP, PSPS
Semantic dementia	SD, svPPA, tvFTD

Clinical syndromes of FTD/Pick complex and their assessment

Frontotemporal dementia: behavioral variant (bvFTD)

Consensus criteria for bvFTD were initially proposed by Neary and colleagues [7] and have recently been revised [13] to reflect advances in imaging, molecular pathology, and genetics. This syndrome is discussed in detail in [Chapter 4](#) but an overview is provided here to illustrate the Pick complex concept. The predominantly behavioral changes often begin with apathy and disinterest, which may be mistaken for depression. On the other hand, the symptoms of disinhibition may suggest a manic psychosis or an obsessive–compulsive or a sociopathic personality disorder [14]. Childish behavior, rudeness, inappropriate sexual remarks, impatience, careless driving, excessive spending or hoarding of certain items, inappropriate joking, perseverative routines, compulsive roaming, insistence of certain foods, excessive food intake, neglect of personal hygiene, disinterest in the immediate family or others are the most characteristic features. The personality change often prompts the family to say that the patient is not the same person any more. Pilfering, shoplifting, swearing, undressing in public, or unexpected urinary and fecal incontinence rapidly bring the patient to the physician, sometimes after the police are involved. When the striking disinhibition and asocial behavior appear, the diagnosis is unmistakable, but neuroimaging is essential to exclude a neoplasm. Standard MRI shows asymmetric frontal atrophy, often more right-sided and variably accompanied by a degree of temporal lobe involvement. Changes first occur in the anterior cingulate and orbitofrontal regions spreading to anterior insular regions and basal ganglia, brain regions modulating emotion and behavior. Later the atrophy spreads to dorsolateral prefrontal regions, leading to a dysexecutive syndrome causing an inability to plan, or carry out

complex tasks. Occasionally such change can be the initial symptom and the patient may be inattentive, impulsive, and distractible. Some of the more advanced behavioral syndromes of bvFTD resemble the so-called Klüver–Bucy syndrome [15]. The syndrome consists of hyperorality (first a sweet tooth, then excessively eating anything), hypersexuality (mostly involving the use of words and gestures), compulsive touching (also called utilization behavior), and disinhibited exploration of the environment. While behavioral disturbance may be an isolated phenomenon initially, the majority develop some degree of progressive aphasia after two to three years which is generally non-fluent but may be fluent and resemble SD (Figure 2.1). Almost a third develop a movement disorder resembling the corticobasal syndrome (CBS) and a separate 10–15% develop features of MND. Conversely, some of the aphasic variants of Pick complex, especially SD, develop the behavior abnormality as a secondary symptom as a rule. The development of these second and third syndromes are characteristic of FTD/Pick complex in our experience and greatly increase the likelihood of FTLD pathology rather than mimics.

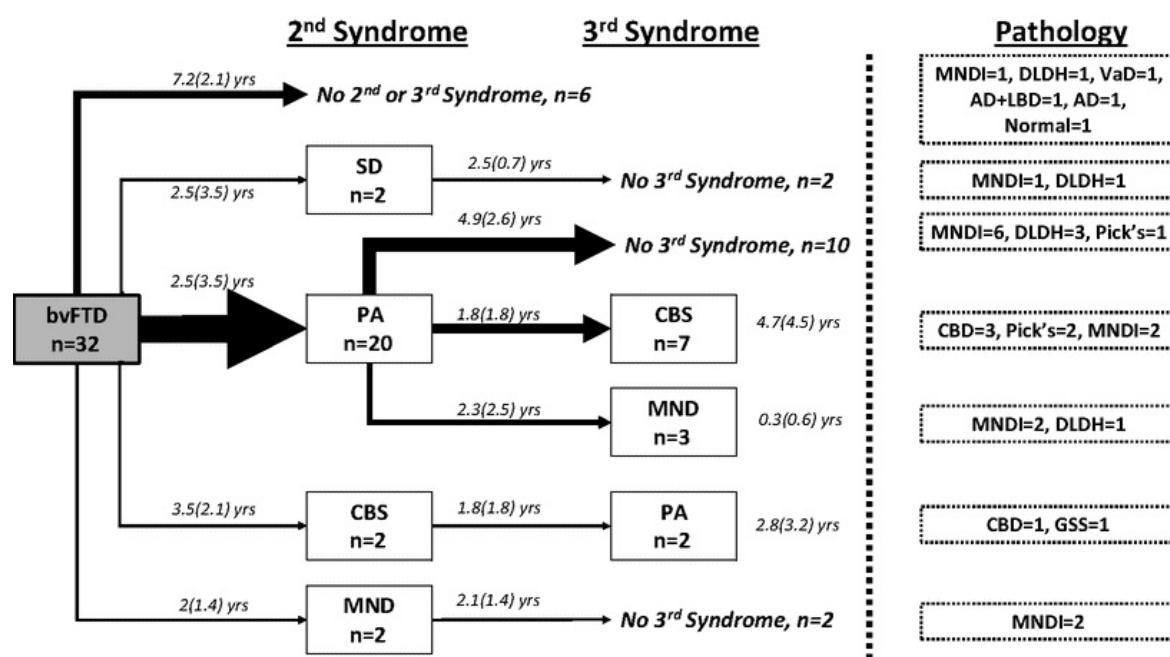


Figure 2.1 Final pathologies, first syndrome, and subsequent evolution

through second and third syndromes in patients from our center presenting initially with bvFTD. Aphasia developing secondarily is indicated as progressive aphasia (PA). Second and third syndromes were CBS, PA, semantic dementia (SD), and MND. The size of the arrows is in proportion to the number of patients at each stage, and the average interval in years (standard deviation) between the syndromes is indicated. Pathologies as follows: MNDI = FTD with motor neuron disease-type inclusions, DLDH = dementia lacking distinctive histology, AD = Alzheimer's disease, VaD = vascular dementia, LBD = Lewy body disease, CBD = corticobasal degeneration, GSS = Gerstmann Straussler Scheinker, Pick's = Pick's disease.

Neuropsychological deficits have been variable because of the types and methods of patient selection at different stages of illness and the tests used [16–18]. The Mini-Mental State Examination (MMSE) may be normal in early cases. Orientation and episodic memory are relatively preserved. Frontal lobe functions are often impaired, yet up to 25% of patients with behavioral presentation perform well on “frontal” tests especially if they are seen early. Although FTD can present as a “dysexecutive syndrome,” frontal lobe or executive deficits are often involved in AD as well. Although FTD is not a memory dominant disorder, the preservation of memory is not universal by any means even in pathologically confirmed cases [19]. The memory complaint in bvFTD could result from inattention, lack of motivation, and/or language impairment. Although drawings in bvFTD patients may be impoverished because of amotivational performance, visuospatial function is generally intact and in advanced cases with mutism, the copying of the intersecting pentagons in the MMSE may be the only element correct. Some patients may be perseverative in drawing. At times copying can be compulsively faithful to detail, even though the patient may not recognize the object drawn in SD. Visuospatial tasks that tap executive function, such as trail-making, are impaired at an early stage, but

block design and Raven's Coloured Progressive Matrices may be preserved. At times, impulsivity, disinhibition, perseveration, echopraxia, and utilization behavior are observed during neuropsychological testing. In later stages the patient may be too restless or language impaired to test.

The caregiver's history and responses to a behavioral questionnaire, such as the Frontal Behavioral Inventory (FBI) [20], at the initial interview are the most useful diagnostic tools. The inventory was designed as a series of structured questions scripted so that both the normal and abnormal aspects of the behaviors were included. Each item was scored on a scale of 4, where 0 = none, 1 = mild or occasional, 2 = moderate, 3 = severe or most of the time. The first group of items were negative behaviors such as apathy, asponaneity, indifference, inflexibility, concreteness, personal neglect, distractibility, inattention, loss of insight, logopenia, verbal apraxia, and alien hand. These last three items were included to capture specific motor and speech behaviors, which may be associated with FTD. The second group of items contained disinhibited behaviors such as perseveration, irritability, jocularity, irresponsibility, inappropriateness, impulsivity, restlessness, aggression, and hyperorality. A cutoff score above 27 was indicative of bvFTD. In our experience reliance on cognitive testing correctly classifies only 75% of cases, increasing to 100% with the addition of the FBI. Discriminant analysis found indifference, impulsivity, and socially inappropriate behavior to be the most diagnostic. Other studies have found roaming, food fads, and stereotypic behavior distinctive. Not all of these behaviors, however, appear in an individual patient and an overall score above the cutoff point on the FBI is probably the most useful confirmatory tool. Longitudinal FBI assessments showed worsening over time. Some behaviors disappear as the patients lose speech or mobility, while others, such as utilization behavior or incontinence, emerge in later stages of the disease.

Primary progressive aphasia (PPA)

Although aphasia with circumscribed frontotemporal atrophy was described by Pick almost a century before, it was redescribed as PPA by Mesulam [8]. Variations of this terminology – particularly progressive non-fluent aphasia (PNFA, nfvPPA) [21] and pure progressive aphemia [22] – have also been used. The condition was considered a separate entity for a while, but evidence emerged to consider it part of FTD/Pick complex [12]. A relatively isolated language disturbance in the first two years of the illness had been suggested by Mesulam as intrinsic to the operational definition of PPA. However, many cases have behavioral or extrapyramidal features, which can appear before the two years are up with FTLD pathology at autopsy (Figure 2.2). Conversely, isolated language disturbance for up to 14 years has been described [23] in some cases. As the initial presentation of PPA is often with word-finding difficulty or anomia, PPA cases may not appear much different to Alzheimer's disease (AD) patients, except for relatively preserved memory and non-verbal cognition [24, 25]. In general though, by the time they show aphasic difficulty, AD patients usually have significant memory loss, disorientation, visuospatial and other cognitive impairments allowing their distinction.

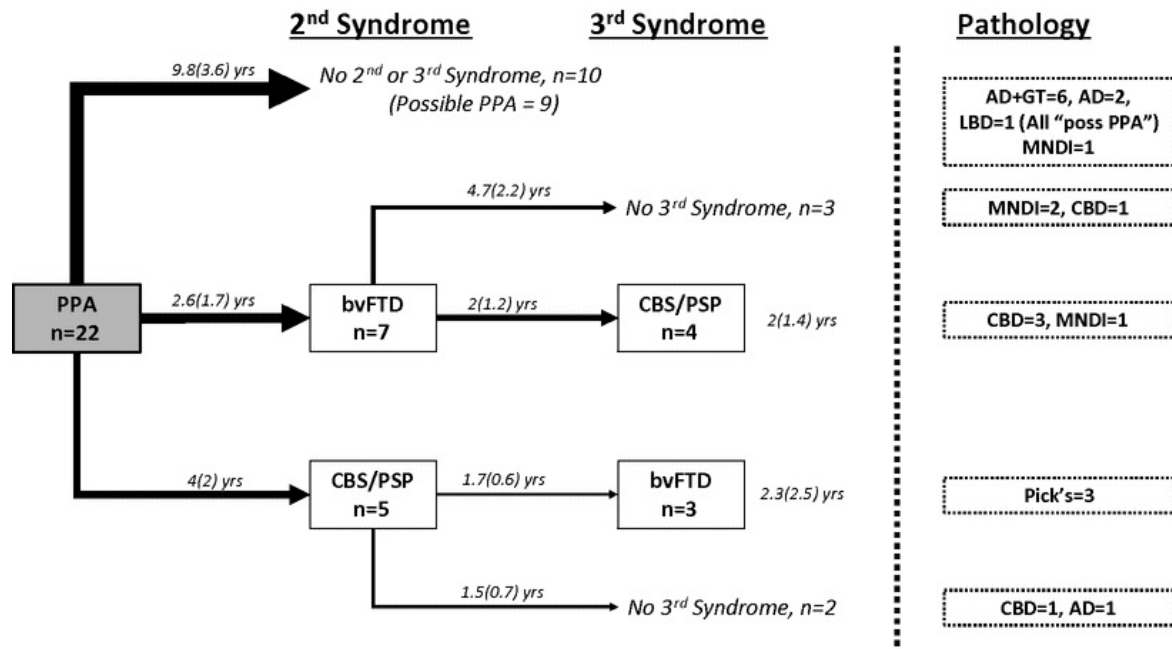


Figure 2.2 Final pathologies, first syndrome, and subsequent evolution through second and third syndromes in patients from our center presenting initially with PPA. The average interval in years (standard deviation) between the syndromes is indicated. Pathologies as follows: AD = Alzheimer's disease, AD+GT = Alzheimer's disease and glial tau, CBD = corticobasal degeneration, LBD = Lewy body disease, GSS = Gerstmann Straussler Scheinker, MNDI = FTD with motor neuron disease-type inclusions, Pick's = Pick's disease.

Spontaneous speech in PPA is slowed with prominent anomia but relatively preserved word knowledge (in contrast to SD), combined with agrammatism (both in production and comprehension) as well as phonemic paraphasias. Some patients present with stuttering or slow, segmented speech and verbal apraxia, which includes articulatory difficulty and phonologic paraphasias which may herald the CBS or PSPS. Recent classification includes apraxia of speech (AOS) within PNFA [26] but a case has been made for this to be considered distinct, when it is a presenting feature [27]. Progressive limb and oro-buccal apraxia can also be a prominent feature [28], further indicating a clinical overlap between PPA and the apraxic-extrapyramidal syndrome of CBD.

MRI is less reliable for diagnosis than in bvFTD or SD but generally there will be asymmetric left hemisphere atrophy centered on the sylvian fissure, inferior frontal regions, anterior insula, and basal ganglia. The course of PPA is variable and may be considerably prolonged, despite a later age of onset [29], but sometimes patients who develop MND or pathology in the basal ganglia progress quickly with difficulty swallowing and choking. The preservation of appropriate social behavior tends to be the rule early on, but in our experience around half of cases develop significant behavioral disturbance as the illness progresses, with features of bvFTD as a secondary or third syndrome (Figure 2.2). Mutism has been considered characteristic of PiD, and it tends to be the end stage of all forms of FTD/Pick complex, even those starting with behavioral abnormalities rather than language disturbance. End-stage mutism also occurs in AD, but usually in a patient who already has global dementia with loss of comprehension and basic functions of daily living [30]. In bvFTD and PPA mutism occurs with relative preservation of comprehension, unlike in a global aphasia or severe AD. Detailed language testing with batteries such as the Western Aphasia Battery (WAB) can be helpful to quantitate fluency, comprehension, repetition, and naming, to determine the type of aphasia and map progression over time.

Semantic dementia (svPPA, semantic aphasia)

A distinct variety of PPA was described as “semantic dementia” by Snowden *et al.* [3]. These patients progressively lose the meaning of words, but retain fluency and are able to carry out a conversation. Subsequent descriptions adopted this term [4], which has recently become the semantic variety of PPA (svPPA). Early descriptions conceptualized the phenomenon as deficit in semantic memory as it involves non-verbal modalities as well

[31]. MRI shows asymmetric atrophy of the anterior temporal lobes, usually left more than right but eventually bilateral and generally accompanied by some frontal atrophy also. Patients with left-predominant atrophy resemble cases of “transcortical sensory aphasia,” in which articulation, phonology, and syntax remain intact but the patient does not comprehend well and has word-finding difficulty. Initially such patients produce semantic substitutions and later fluent semantic jargon, often totally irrelevant to the questions asked or the topics discussed. Category-specific anomia is characteristic, often for living things before man-made objects or tools. Superordinate categories are used in place of specific items, so for example an “eagle” will be called a “bird” then a “creature” before all naming ability is lost. Patients with SD tend to differ significantly from the fluent aphasics of AD because of relatively preserved episodic and autobiographical memory, and visuospatial tasks tend to be well performed. They or their caregivers may complain of memory loss but closer questioning generally reveals this to be a form of word-finding and comprehension difficulty. Irregularly pronounced words will be read incorrectly as they can not be processed by meaning (surface dyslexia). SD is distinct from AD not by virtue of retained fluency, but by an early prominent deficit in noun comprehension followed by a visual agnosia and also by its frequent association with bvFTD, especially if the right temporal lobe is involved. Conversely, patients who present with the behavioral symptoms of bvFTD often have elements of SD at initial assessment or they emerge with time as a second or third syndrome of the Pick complex.

The behavior in SD can be so dissociative and bizarre that some of these patients are considered hysterical or schizophrenic. Compulsive behaviors are the norm but may be delayed, with the pattern determined by the side affected. The left-sided cases tend to focus on visually attractive items such as coins and card playing while right-sided cases tend towards

word puzzles and writing. As the right side becomes affected, problems recognizing emotions in others emerge along with inability to recognize familiar faces (prosopagnosia) and buildings. Eventually a multimodality agnosia emerges and in our cohort a third of SD patients had a loss of the meaning of objects in the visual and tactile domains in addition to the usual auditory deficit.

Logopenic variant of PPA (lvPPA)

Subsequently a new variety of PPA was proposed [32]. Logopenia is defined as prominent word-finding difficulty, a phrase length still longer than four words, and preserved syntax while repetition is disproportionately impaired reflecting deficits in verbal working memory [33]. It is argued that logopenic PPA (LPA) tends to involve more posterior perisylvian structures on MRI such as angular and supramarginal gyri, which is consistent with the overrepresentation of underlying AD pathology in this form of PPA [34], but the predictive value of LPA may be limited compared with other variants [35].

Corticobasal degeneration (CBD) and progressive supranuclear palsy PSP)

There have been several case descriptions of PiD where the patients had prominent extrapyramidal features [36]. Sometimes unilateral rigidity and parkinsonism were the first symptoms to attract attention and it was recognized that subcortical changes occur in PiD, even without overt extrapyramidal symptomatology [37]. When Rebeiz *et al.* [38] described corticodentatonigral degeneration, they recognized the similarity of the pathology to PiD. The clinical syndrome of unilateral rigidity, prominent apraxia, gaze palsy, reflex myoclonus, and the alien hand syndrome was

relabeled CBD [10]. Some case reports have described patients with clinical features of CBS as defined by unilateral rigidity, apraxia, and alien hand syndrome but who had the pathologic findings of PiD with Pick bodies [39]. Other cases pathologically typical of CBD have had bvFTD or PPA without the extrapyramidal features [40]. We suggested that the clinical syndrome of prominent apraxia, unilateral extrapyramidal syndrome, and alien hand phenomenon should be designated as corticobasal degeneration syndrome (CBDS), and CBD should be used for the pathologic picture [41] (CBS is the other abbreviation for the clinical syndrome most used currently, but it is less easily recognizable and it does not parallel the frequently used PSPS). CBS has shown significant overlap with the syndromes of FTD/Pick complex [42] and in recognition of that, recently proposed criteria [43] recognize four CBD phenotypes, namely the corticobasal syndrome (CBS), a frontal behavioral-spatial syndrome (FBS), the non-fluent/agrammatic variant of primary progressive aphasia (naPPA), and progressive supranuclear palsy syndrome (PSPS).

The syndrome of axial dystonia, bradykinesia, falls, dysphagia, and vertical gaze palsy was described as PSP by the Toronto group of Steele *et al.* [9], but the overlap with CBD/CBS has been increasingly recognized. Many CBD/CBS patients also have vertical gaze palsy; some have falls and symmetrical extrapyramidal syndrome. Some studies comparing the neuropsychological features of PSPS and CBS found no significant difference between them [44]. The pathologic, biochemical, and genetic features of PSP/CBD also overlap to a great extent [45, 46]. They are both considered to be predominantly 4 repeat tauopathies and have common tau haplotypes. There is continuing controversy to what extent PSP/PSPS and CBD/CBS can be differentiated, although pathologic criteria for each have been validated [47] and the evidence therefore very much favors that both are part of the FTD/Pick complex.

Motor neuron disease and FTD (FTD-MND)

In the 1980s and 1990s reports emerged integrating an association between dementia and MND/ALS (amyotrophic lateral sclerosis) [48, 49] into the concept of FTD but as with most phenomenology in FTD/Pick complex, precedence lies much earlier [50]. Cognitive and behavioral impairment has been observed in ALS and some estimate it to be as high as 50% [51, 52]; conversely features of MND occur in 15% of those with FTD/Pick complex. A characteristic finding in FTD-MND cases is the presence of psychotic features such as delusions and hallucinations which are relatively rare in most other FTD/Pick complex syndromes, certainly when compared with Alzheimer's disease or dementia with Lewy bodies (DLB). Combined with prominent apathy, lack of motivation, and irritability it meant such cases were often erroneously diagnosed as depression before the motor features emerged, which they usually do within a year. Dysphagia and dysarthria are common with a severe progressive non-fluent aphasia ending in mutism for a significant number of cases of FTD-MND [49]. The illness course is rapid with a very poor prognosis and median survival of two years in florid cases [53].

Beyond shared clinical features, overlap on a molecular level was demonstrated by cases of dementia and MND with ubiquitin-positive, tau-negative inclusions in the cortex, which had been previously described in the motor neurons of ALS cases [54]. Subsequently these cases were named motor neuron disease inclusion dementia (MNDID) [55] and in the majority it has become apparent that these ubiquitinated inclusions contain transactive response DNA-binding protein 43 (TDP-43) as the main pathologic protein. A shared genetic overlap was shown in 2006 with linkage to chromosome 9p in FTD-MND families. Some family members developed MND alone, others pure FTD, and others again a mixture of both

FTD and MND [56, 57]. A hexanucleotide repeat expansion in the non-coding region of *C9orf72* gene was found to be causative [58, 59], generally resulting in TDP-43-positive pathology, thalamic atrophy, and a high prevalence of psychosis. *C9orf72* is now known to be the commonest genetic cause of MND and FTD in those of European descent accounting for up to 14% of all sporadic and familial MND [60]. It is estimated that *C9orf72* mutations account for 5–6% of sporadic FTD and up to 25% of familial cases, and preliminary evidence suggests a positive relation between repeat size in frontal cortex and age of onset but an inverse relation between repeat size (in the cerebellum only) and survival [61].

Neuropathology and molecular genetics

Pathology

Even more so than the clinical syndromes, pathology in FTLD is diverse, but has a great deal of morphologic and biologic overlap. Differences in the topographic distribution of the pathology determine the individual clinical syndromes within the Pick complex. Common to all, the gross macroscopic pathology consists of variable atrophy of the frontal and anterior temporal lobes with a shared histology of large neuronal cell loss, microvacuolation, and varying degrees of gliosis. Immunohistochemistry in the last decade has allowed the subcategorization of these disorders into various proteinopathies based on the major constituent of the inclusions and these are summarized in Table 2.2. Additional details on the neuropathology of FTLD are provided in Chapter 13.

Table 2.2 Molecular pathology subtypes in FTD/Pick complex

Molecular pathologies in FTLD	Associated
-------------------------------	------------

FTLD-TAU (TAU-POSITIVE)**FTLD-tau (40%)***MAPT*

Argyrophilic grain disease (AGD)

Corticobasal degeneration (CBD)

FTLD with microtubule- associated tau mutations
(FTLD-*MAPT*)

Neurofibrillary tangle dementia (NFTD)

Pick's disease (PiD) Progressive supranuclear palsy
(PSP)Sporadic multiple system tauopathy with dementia
(MSTD)White matter tauopathy with globular glial inclusions
(WMT-GGI)**FTLD-U (TAU-NEGATIVE, UBIQUITIN-POSITIVE)****FTLD-TDP types A to D [\[64\]](#) (50%)***TARDBP*

Type A

GRN

Type B

C9orf72

Type C

Type D

*VCP***FTLD-fused in sarcoma (FUS) (5%)***FUS*

Atypical FTLD with ubiquitin inclusions (aFTLD-U)

Basophilic inclusion body disease (BIBD)

Neuronal intermediate filament inclusion disease

(NIFID)

**FTLD with immunochemistry against ubiquitin
proteasome system (FTLD-UPS) (5%)**

CHMP2B

**FTLD WITH NO INCLUSIONS Dementia lacking
distinctive histology (DLDH)**

Historically speaking most neuropathologists required Pick bodies (intracytoplasmic argyrophilic inclusions) for the diagnosis of Pick's disease as seen by light microscopy with the Bielschowsky silver stain. Constantinidis *et al.* [[11](#)] labeled Pick-body-positive cases as Pick type A. Those with absent Pick bodies but swollen achromatic neurons called “Pick cells,” which also contain tau protein, are Pick type B (these cases are now labeled CBD). Pick cells may occur in patients with typical Pick bodies as well and they are typical of CBD. These cases and PSP have a predominantly tau abnormality and are now labeled together as FTLD-T (for tau). Pick type C consists of neuronal loss, vacuolation in upper cortical layers, and extensive astrogliosis of the neocortex, and these changes are common to all histologic subtypes.

In the last decade it became apparent that the most common pathology of FTD/Pick complex had the ubiquitin-positive, tau-negative inclusions previously described in MND [[54](#)]. These inclusions (often abbreviated to FTD-MND type or MNDI or FTLD-U) were found in more than half of the FTD cases at autopsy [[29](#), [62](#)]. They appeared similar in location and morphology to Pick bodies, but differed in their histochemical characteristics. The more recent discovery of TDP-43 immunohistochemistry as the underlying protein in FTLD-U changed the concept of a ubiquinopathy as the most common pathologic and biologic variety of FTD/Pick complex to a “TDP43-pathy” instead [[63](#)]. As demonstrated in the initial reports and rapidly confirmed by numerous

subsequent studies, antibodies against TDP-43 have proven to be the most sensitive and specific tool to detect most of the different types of ubiquitin-positive pathology found in most cases of FTLD-U, including the neuronal cytoplasmic inclusions (NCIs) and neuronal intranuclear inclusions (NIIs). Different classification systems for FTLD-TDP exist but most recently a harmonized system defining four subtypes (types A–D) has been proposed [64].

Not all FTLD-U cases have the TDP-43 proteinopathy. The TDP-43-negative cases (also known as atypical FTLD-U [aFTLD-U], basophilic inclusion body disease [BIBD] and neuronal intermediate filament inclusion disease [NIFID]) have been shown to have antibodies to the fused in sarcoma (FUS) protein [65, 66]. Together they comprise a new biochemical category of neurodegenerative disease the “FUS proteinopathies.” Atypical FTLD-U is characterized by a very early onset of severe behavioral abnormality without motor deficits or aphasia. The consistent involvement of motor neurons in BIBD indicates that the association of FTLD and MND/ALS can occur on a FUS or TDP-43 pathologic substrate.

There is substantial overlap between all pathologic varieties, although their distinctiveness is also argued [45, 67]. Various purportedly distinctive features, such as Pick bodies in PiD, astrocytic plaques in CBD, tufted astrocytes in PSP, and ubiquitin-positive, tau-negative inclusions in MND-type dementia, are described, but they can occur with each of the other clinical varieties. The TDP-43 protein abnormality is present in ALS but also in about 20% of AD, so the specificity of that too remains to be determined. Equally, for genetic cases correlations with pathology are not absolute and cases of tau-positive CBD pathology presenting with FTD and parkinsonism but without MND have been found in some *C9orf72* families [68].

A basic dichotomy lies between tau-positive (FTLD-tau) and FTLD-U. FTLD-tau accounts for approximately 40% of FTLD and includes classical Pick's disease, CBD, PSP, FTLD associated with tau mutations (FTLD-T), argyrophilic grain disease, neurofibrillary tangle dementia (NFTD), and multiple system tauopathy with dementia (MSTD). FTLD-U accounts for approximately 50% of FTLD and is subclassified as FTLD-TDP (TDP-43), FTLD-FUS (fused in sarcoma), and FTLD-UPS (ubiquitin proteasome system (i.e., ubiquitinated inclusions negative for tau, TDP-43, and FUS). FTLD-TDP accounts for 85–90% of all FTLD-U and is subdivided into four subtypes A–D [64]. FTLD-FUS includes aFTLD-U, NIFID, and BIBD. Cases without signature protein histochemistry, the so-called dementia lacking distinctive histology (DLDH), were previously a prominent substrate in pathology cohorts but now comprise an ever-dwindling designation.

Genetic relationships

A family history of degenerative dementia, often autosomal dominant, is detected in 25–50% of cases. In 1998 the first identified causative gene for FTD/Pick complex was the microtubule-associated protein tau (*MAPT*) gene on chromosome 17. Since then multiple new genes have been identified, including progranulin (*GRN*), valosin-containing protein, (*VCP*), *FUS*, *TARDBP*, charged multivesicular protein (*CHMP2B*), and most recently *C9orf72*. *GRN* and *C9orf72* account for the largest proportion of FTD/Pick complex families, followed by *MAPT*; *VCP* causes the rare combination of FTD, inclusion body myopathy, and Paget's disease of bone, highlighting yet another overlap with heterogeneous neurodegenerative disease. *TARDBP* mutations account for 5% of familial ALS but only a handful of FTD kindreds. Each gene is associated with a particular

pathology: *MAPT* with FTLD-tau; *GRN*, *C9orf72*, *TARDBP*, and *VCP* with FTLD-TDP; *FUS* mutations cause FTLD-FUS; and *CHMP2B* causes FTLD-UPS [69]. Additional details on the genetics of FTLD are reviewed in [Chapter 14](#).

Clinicopathologic correlations in FTD/Pick complex

Our autopsy experience in FTD/Pick complex is summarized in [Figures 2.1–2.3](#). Among the 58 autopsied patients with probable FTD/Pick complex, the diagnosis was confirmed pathologically in 50, whereas in 8 cases, 6 of them in the bvFTD group, the pathologic diagnosis was different: 2 AD + DLB, and 1 each of AD, vascular dementia, prion disease, and normal histology, as were 2 in the PPA group (AD and AD + DLB). All the possible PPA cases (they were also given an alternative diagnosis of AD in vivo) coming to autopsy received a pathologic diagnosis outside the FTD/Pick complex: AD in eight cases and DLB in one. Some of these cases turned out to have argyrophilic tau astrocyte clusters (ATAC), suggesting a double pathology of coexisting AD and a Pick complex tauopathy [70]. The diagnosis of probable FTD in our clinic has a positive predictive value (accuracy) of 87%. A chi square comparison showed that multiple syndromes predicted FTD/Pick complex pathology to a much greater extent than did a single syndrome ($p < 0.001$). In our experience the clinical varieties of Pick complex do not predict the overall pathologic spectrum, but some generalizations can be made. There is a prominence of tau-positive CBD or Pick body pathology (FTLD-tau) in the extrapyramidal and aphasic presentations, and the FTLD-U-type with the behavioral presentation and SD [29]. Further insights can be derived from

histochemical profiles [71, 72]. The behavioral variant of FTD is associated with all histochemical and genetic subtypes but more than half will be caused by FTLD-TDP. The movement disorder of PSP/CBD predominantly aggregates with the expected tau-positive pathology but is also seen with FTLD-TDP and rarely with FTLD-FUS (NIFID) [73]. Two thirds of PNFA will be due to tau-positive pathology of CBD, PSP, and PiD particularly if associated with apraxia of speech, but PNFA is also seen with FTLD-TDP type A and B though probably not FTLD-FUS. SD is the most unitary of FTD/Pick complex syndromes and is associated most consistently with FTLD-TDP type C and to a lesser extent type B and PiD. Most logopenic PPA cases have AD pathology [34] as do cases with both output and comprehension difficulty (mixed aphasia). FTD-MND can be seen with tau mutations but overwhelmingly is associated with FTLD-TDP, typically type C, and infrequently FTLD-FUS. FTLD-FUS is associated with very young-onset bvFTD, psychosis, thought and mood disorders, with prominent caudate atrophy on imaging [74]. Increasing evidence of phenotypic heterogeneity of *C9orf72* – including prominent psychotic symptoms, aphasia, and parkinsonism [75] – poses challenges in the future.

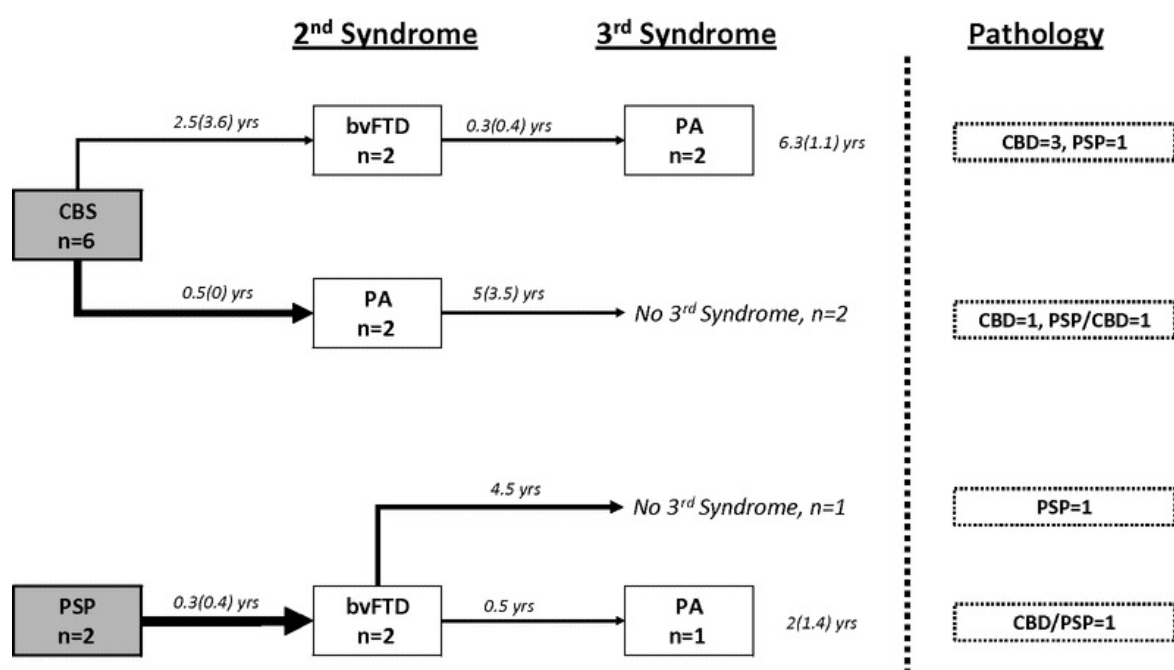


Figure 2.3 Final pathologies, first syndrome, and subsequent evolution through second and third syndromes in patients from our center presenting initially with CBD and PSP. Pathologies as follows: CBD = corticobasal degeneration, PSP = progressive supranuclear palsy, CBD/PSP = transitional features of both.

Differential diagnosis

Alzheimer's disease

The typical presentation of AD in an elderly patient with a progressive amnesic syndrome combined with some degree of visuospatial and executive dysfunction rarely presents diagnostic difficulty. Similarly for bvFTD the reports of inappropriate behaviors, a lack of empathy, stereotypies, and changes in eating preference help differentiate it from AD [76]. However, focal variants of AD frequently enter the differential for all the FTD/Pick complex clinical syndromes, with 10–20% of cases in autopsy series meeting criteria for bvFTD but turn out to have Alzheimer's pathology. Recently revised criteria for bvFTD relax the exclusion criteria somewhat to accommodate the phenotypic variability of FTLD but it has been suggested this may increase the false-positive rate [77]. In general, though, AD mimics show additional features of memory impairment and/or mild visuospatial impairment within the first one to three years which help distinguish them [78]. There are of course exceptions and severe amnesia has been described in cases with proven FTLD pathology, resulting in diagnoses of AD in life [19] even in specialist centers. In our experience the failure to develop a second or third Pick complex syndrome reliably identified the non-FTLD cases and AD in particular (Figures 2.1–2.3) but that feature may not be evident until several years into their illness.

Progressive aphasia is probably the Pick complex syndrome most likely to contain AD mimics which comprise the majority of cases with logopenic PPA and a substantial minority of PNFA but relatively few SD. Differentiation can be particularly difficult after the early stages of PPA when more widespread cognitive domains are involved. Logopenic aphasia, prominent phonologic errors, mixed aphasia, later age of onset, and memory complaints evident with follow-up point to underlying AD pathology [78].

AD can also mimic the movement disorder/parietal syndrome of CBS. AD can be the underlying pathology even in apparently prototypical cases of CBS with severe apraxia and extrapyramidal signs including alien limb phenomena. To add to the difficulty, dopamine transporter scanning can be normal in pathologically proven cases of CBD and so cannot always be relied upon to differentiate pathologies [79]. It has been suggested that a number of clinical features, such as early memory complaints and memory/orientation deficits on cognitive batteries versus frontal behaviors, non-fluent language, and oro-buccal apraxia, differentiate AD from CBD pathology in vivo [80], but this finding has not been replicated [81].

In addition to Alzheimer's mimicking FTD/Pick complex on a clinical level, mutations in presenilin 1 (PS1), the main genetic cause of familial AD, have been described in several families with apparently typical bvFTD [82]. In some cases this has been with typical AD pathology, reflecting a focal variant of the disease. In others the PS1 mutations have been associated with mixed AD and Pick pathology [83] or even classical Pick's disease in the absence of amyloid accumulation [84], suggesting PS1 mutations may predispose to both diseases by affecting amyloid precursor protein (APP) and/or tau processing. Differentiation of AD and FTLD may be aided by the increasing use of cerebrospinal fluid (CSF) biomarkers of neurodegeneration in diagnosis, perhaps to be complemented by molecular imaging techniques such as amyloid or tau PET. Lower CSF total tau to

amyloid A β 1–42 ratios have been demonstrated in FTL D compared with AD, differentiating the two with sensitivities and specificities over 90% [85], though for now such techniques are largely confined to research centers.

Vascular dementia

Apathy, abulia, and a dysexecutive syndrome are features common to both bvFTD and vascular dementia (VaD) and may cause confusion but disinhibition, stereotypies, and altered eating behaviors are less prominent in VaD [86]. The timing of a stroke usually makes the diagnosis clear but caregiver recall can be unreliable and the stepwise decline – once thought pathognomonic of a vascular etiology – may be absent. A slowly progressive aphasia would be distinctly unlikely for VaD, which more typically causes one of the classical aphasic syndromes such as Broca's or Wernicke's with only a superficial resemblance to the non-fluent and fluent types of PPA. A prior history of stroke disease combined with other vascular risk factors, pyramidal signs, and appropriately located lesions on MRI usually removes diagnostic doubt.

Prion disease

Human prion diseases, also known as transmissible spongiform encephalopathies, comprise a varied group of neurodegenerative disorders classified according to etiology as sporadic, inherited, or acquired/iatrogenic. The typical presentation is a rapidly progressive dementia with ataxia and myoclonus but many variants are described. Focal onset is not unusual early on in sporadic Creutzfeldt–Jakob disease and there are several reports of progressive aphasia due to prion disease in the literature, but this typically evolves rapidly to a generalized dementia with

myoclonus and EEG changes before death one to two years from onset [87]. Clinicopathologic series of clinically defined FTD cohorts contain a smattering of prion cases mimicking FTD [29, 88]. Of all prion diseases the inherited forms can be particularly diverse with reports of different phenotypes in different siblings and some diagnosed as Pick's disease and FTD before the genetic abnormality was recognized [89]. The authors have experience of a man in his 50s developing behavioral disturbance meeting criteria for bvFTD that evolved into a progressive aphasia and then a generalized dementia for six to seven years before the appearance of myoclonic jerks in the terminal phase. An octapeptide repeat insertion in the prion protein gene was detected and prion pathology confirmed at autopsy.

Psychiatric phenocopies

Researchers in Cambridge, UK identified several cases, almost always male, meeting criteria for bvFTD who appear not to progress, may in fact improve, and survive for prolonged periods. They are distinguished by a normal or near normal performance on executive tests, memory, and social cognition; activities of daily living are preserved and both structural and functional imaging are normal [90]. The phenocopy syndrome is controversial and the cause unclear but proposed etiologies include low-grade chronic mood disorders and decompensated personality disorders perhaps from the Asperger's spectrum [91]. A neurodegenerative dementia seems unlikely based on the few cases in Cambridge to have come to autopsy since they do not have FTLD pathology. There is circumstantial evidence from elsewhere to support the phenocopy theory as bvFTD cases with normal brains at autopsy were identified in two large pathology cohorts from other centers [29, 88]. Our pathology cohort included one bvFTD patient who died in a road traffic accident and had a normal brain at

autopsy, though only one hemisphere was examined [29]. Characteristically for non-FTLD cases no second or third Pick complex syndrome developed in this individual. The need to account for such anomalous cases is implicit in revised bvFTD criteria, requiring evidence of progression and imaging abnormalities for “probable” as opposed to “possible cases” [13].

Conclusions

The wheel has been reinvented several times in FTD/Pick complex over the years as modern researchers have rediscovered and renamed the clinical syndromes already detailed with remarkable prescience by their forebears. Though initially described as either an aphasic and/or behavioral syndrome our understanding of FTD/Pick complex has been greatly enriched by careful observations detailing the overlap with other degenerative disorders. Recognition of these relationships has brought new insights, challenged accepted wisdom, and opened new lines of investigation leading to the discovery of shared pathologic pathways for the aphasic, behavioral, amyotrophic, and extrapyramidal syndromes of the Pick complex. Initially a controversial finding [42] but now accepted wisdom, a clear path follows from the description of patients with rigid apractic movement disorders emerging from a progressive aphasia leading to the discovery of CBD as the common pathology in PPA. The development of amyotrophy in FTD, and the shared presence of ubiquitinated inclusions in FTLD and MND led logically to the discovery of *C9orf72* as a major gene in both disorders and the tantalizing prospect of realistic targets for disease-modifying targets in the next few years.

In conclusion, the syndromes of FTD/Pick complex, though initially distinct, converge over time, and can be the manifestation of different

histologic varieties. The most convincing distinction is between the behavioral and semantic dementia (bvFTD, svPPA) patient with tau-negative, ubiquitin-positive (TDP-43- or FUS-positive) inclusions and the nfvPPA cases (with or without CBD/PSP syndrome) due to tau-positive pathology. There is, however, considerable clinical and pathologic overlap to consider them distinct diseases. The molecular and histopathologic differences between the pathologic varieties are interesting and important biologically but the clinical features overlap and do not entirely predict the tau versus ubiquitin/TDP dichotomy. The differences between the clinical presentations are nonetheless important for diagnosis, and management. Many of the differences we do see can be attributed to the topographic distribution of pathology yet there are emerging relationships between histochemistry and localization that offer a realistic prospect of targeting future disease-modifying therapies to a predictable pathology, perhaps for genetically defined cohorts initially. Nevertheless all syndromes can occur with all of the histologic varieties and the complex is best viewed as one disease rather than many. Accurate description at various levels is important. Overclassification hampers the recognition of the underlying biologic and clinical disease and creates unwieldy terminologic proliferation. However, at the same time the recognition of its biologic diversity is necessary for progress and more specific treatment.

References

1. Pick A. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prag Med Wochenschr* 1892;**17**:165–7.
2. Pick A. Zur symptomatologie der linksseitigen Schlafenlappenatrophie. *Monatsschr Psychiatr Neurol* 1904;**16**:378–88.

-
3. Snowden J, Goulding P, Neary D. Semantic dementia: a form of circumscribed cerebral atrophy. *Behav Neurol* 1989;**2**:167–82.
-
4. Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain* 1992;**115**(Pt 6):1783–806.
-
5. Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. *Arch Gerontol Geriatr* 1987;**6**(3):193–208.
-
6. Neary D, Snowden JS, Northen B, Goulding P. Dementia of frontal lobe type. *J Neurol Neurosurg Psychiatry* 1988;**51**(3):353–61.
-
7. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;**51**(6):1546–54.
-
8. Mesulam MM. Primary progressive aphasia – differentiation from Alzheimer's disease. *Ann Neurol* 1987;**22**(4):533–4.
-
9. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* 1964;**10**:333–59.
-
10. Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. *Brain* 1989;**112**(Pt 5):1171–92.
-
11. Constantinidis J, Richard J, Tissot R. Pick's disease. Histological and clinical correlations. *Eur Neurol* 1974;**11**(4):208–17.
-
12. Kertesz A, Hudson L, Mackenzie IR, Munoz DG. The pathology and nosology of primary progressive aphasia. *Neurology* 1994;**44**(11):2065–72.
-
13. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus

J, *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;**134**(Pt 9):2456–77.

14. Gregory CA, Hodges JR. Clinical features of frontal lobe dementia in comparison to Alzheimer's disease. *J Neural Transm Suppl* 1996;**47**:103–23.

15. Cummings JL, Duchen LW. Kluver-Bucy syndrome in Pick disease: clinical and pathologic correlations. *Neurology* 1981;**31**(11):1415–22.

16. Miller BL, Cummings JL, Villanueva-Meyer J, Boone K, Mehninger CM, Lesser IM, *et al.* Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. *Neurology* 1991;**41**(9):1374–82.

17. Elfgrén C, Passant U, Risberg J. Neuropsychological findings in frontal lobe dementia. *Dementia* 1993;**4**(3–4):214–19.

18. Hodges JR, Patterson K, Ward R, Garrard P, Bak T, Perry R, *et al.* The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology* 1999;**13**(1):31–40.

19. Graham A, Davies R, Xuereb J, Halliday G, Kril J, Creasey H, *et al.* Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* 2005;**128**(Pt 3):597–605.

20. Kertesz A, Davidson W, McCabe P, Munoz D. Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia. *Alzheimer Dis Assoc Disord* 2003;**17**(4):223–9.

21. Grossman M, Mickanin J, Onishi K, Hughes E, D'Esposito M, Ding XS, *et al.* Progressive nonfluent aphasia: language, cognitive, and PET measures contrasted with probable Alzheimer's disease. *J Cogn Neurosci* 1996;**8**(2):135–54.

22. Cohen L, Benoit N, Van Eeckhout P, Ducarne B, Brunet P. Pure progressive

aphemia. *J Neurol Neurosurg Psychiatry* 1993;**56**(8):923–4.

23. Mesulam MM, Grossman M, Hillis A, Kertesz A, Weintraub S. The core and halo of primary progressive aphasia and semantic dementia. *Ann Neurol* 2003;**54** Suppl 5:S11–14.

24. Karbe H, Kertesz A, Polk M. Profiles of language impairment in primary progressive aphasia. *Arch Neurol* 1993;**50**(2):193–201.

25. Weintraub S, Rubin NP, Mesulam MM. Primary progressive aphasia. Longitudinal course, neuropsychological profile, and language features. *Arch Neurol* 1990;**47**(12):1329–35.

26. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, *et al.* Classification of primary progressive aphasia and its variants. *Neurology* 2011;**76**(11):1006–14.

27. Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Master AV, *et al.* Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. *Brain* 2012;**135**(Pt 5):1522–36.

28. Fukui T, Sugita K, Kawamura M, Shiota J, Nakano I. Primary progressive apraxia in Pick's disease: a clinicopathologic study. *Neurology* 1996;**47**(2):467–73.

29. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain* 2005;**128**(Pt 9):1996–2005.

30. Appell J, Kertesz A, Fisman M. A study of language functioning in Alzheimer patients. *Brain Lang* 1982;**17**(1):73–91.

31. Whiteley AM, Warrington EK. Prosopagnosia: a clinical, psychological, and anatomical study of three patients. *J Neurol Neurosurg Psychiatry* 1977;**40**(4):395–403.

32. Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, *et al.* Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol* 2004;**55**(3):335–46.

33. Mesulam M, Weintraub S. Primary progressive aphasia: sharpening the focus on a clinical syndrome. In: Boller F, Forrette F, Khachaturian Z, Poncet M, Christen Y, editors. *Heterogeneity of Alzheimer's Disease* Berlin: Springer-Verlag; 1992. p. 43–66.

34. Mesulam M, Wicklund A, Johnson N, Rogalski E, Léger GC, Rademaker A, *et al.* Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Ann Neurol* 2008;**63**(6):709–19.

35. Harris JM, Gall C, Thompson JC, Richardson AM, Neary D, du Plessis D, *et al.* Classification and pathology of primary progressive aphasia. *Neurology* 2013;**81**(21):1832–9.

36. Akelaitis AJ. Atrophy of basal ganglia in Pick's disease. A clinicopathologic study. *Arch Neurol Psychiatr* 1944;**51**:27–34.

37. Munoz-Garcia D, Ludwin SK. Classic and generalized variants of Pick's disease: a clinicopathological, ultrastructural, and immunocytochemical comparative study. *Ann Neurol* 1984;**16**(4):467–80.

38. Rebeiz JJ, Kolodny EH, Richardson EP. Corticodentatonigral degeneration with neuronal achromasia. *Arch Neurol* 1968;**18**(1):20–33.

39. Lang AE, Bergeron C, Pollanen MS, Ashby P. Parietal Pick's disease mimicking cortical-basal ganglionic degeneration. *Neurology* 1994;**44**(8):1436–40.

40. Lippa CF, Smith TW, Fontneau N. Corticonigral degeneration with neuronal achromasia. A clinicopathologic study of two cases. *J Neurol Sci* 1990;**98**(2–3):301–10.

-
- 41.** Kertesz A, Munoz DG. *Pick's Disease and Pick Complex* New York; Chichester: J. Wiley & Sons; 1998.
-
- 42.** Kertesz A, Martinez-Lage P, Davidson W, Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. *Neurology* 2000;**55**(9):1368–75.
-
- 43.** Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, *et al.* Criteria for the diagnosis of corticobasal degeneration. *Neurology* 2013;**80**(5):496–503.
-
- 44.** Pillon B, Blin J, Vidailhet M, Deweer B, Sirigu A, Dubois B, *et al.* The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. *Neurology* 1995;**45**(8):1477–83.
-
- 45.** Feany MB, Mattiace LA, Dickson DW. Neuropathologic overlap of progressive supranuclear palsy, Pick's disease and corticobasal degeneration. *J Neuropathol Exp Neurol* 1996;**55**(1):53–67.
-
- 46.** Houlden H, Baker M, Morris HR, MacDonald N, Pickering-Brown S, Adamson J, *et al.* Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. *Neurology* 2001;**56**(12):1702–6.
-
- 47.** Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, *et al.* Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. *J Neuropathol Exp Neurol* 2002;**61**(11):935–46.
-
- 48.** Mitsuyama Y. Presenile dementia with motor neuron disease in Japan: clinico-pathological review of 26 cases. *J Neurol Neurosurg Psychiatry* 1984;**47**(9):953–9.
-
- 49.** Neary D, Snowden JS, Mann DM, Northen B, Goulding PJ, Macdermott N. Frontal lobe dementia and motor neuron disease. *J Neurol Neurosurg Psychiatry*

1990;**53**(1):23–32.

50. Von Braumuhl A. Picksche krankheit und amyotrophische lateralsklerose. *Allgemeine Z Psychiatr Psychol Med* 1932;**96**:364–6.

51. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 2002;**59**(7):1077–9.

52. Strong MJ, Lomen-Hoerth C, Caselli RJ, Bigio EH, Yang W. Cognitive impairment, frontotemporal dementia, and the motor neuron diseases. *Ann Neurol* 2003;**54** Suppl 5:S20–3.

53. Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. *Neurology* 2003;**61**(3):349–54.

54. Okamoto K, Hirai S, Yamazaki T, Sun XY, Nakazato Y. New ubiquitin-positive intraneuronal inclusions in the extra-motor cortices in patients with amyotrophic lateral sclerosis. *Neurosci Lett* 1991;**129**(2):233–6.

55. Jackson M, Lennox G, Lowe J. Motor neurone disease-inclusion dementia. *Neurodegeneration* 1996;**5**(4):339–50.

56. Morita M, Al-Chalabi A, Andersen PM, Hosler B, Sapp P, Englund E, *et al.* A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology* 2006;**66**(6):839–44.

57. Vance C, Al-Chalabi A, Ruddy D, Smith BN, Hu X, Sreedharan J, *et al.* Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2–21.3. *Brain* 2006;**129**(Pt 4):868–76.

58. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;**72**(2):245–56.

-
- 59.** Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;**72**(2):257–68.
-
- 60.** Anderson P. ALS and FTD: two sides of the same coin? *Lancet Neurol* 2013;**12**:937–8.
-
- 61.** van Blitterswijk M, DeJesus-Hernandez M, Niemantsverdriet E, Murray ME, Heckman MG, Diehl NN, *et al.* Association between repeat sizes and clinical and pathological characteristics in carriers of *C9ORF72* repeat expansions (Xpansize-72): a cross-sectional cohort study. *Lancet Neurol* 2013;**12**(10):978–88.
-
- 62.** Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, *et al.* Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* 2004;**56**(3):399–406.
-
- 63.** Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, *et al.* Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;**314**(5796):130–3.
-
- 64.** Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, *et al.* A harmonized classification system for FTLTDP pathology. *Acta Neuropathol* 2011;**122**(1):111–13.
-
- 65.** Munoz DG, Neumann M, Kusaka H, Yokota O, Ishihara K, Terada S, *et al.* FUS pathology in basophilic inclusion body disease. *Acta Neuropathol* 2009;**118**(5):617–27.
-
- 66.** Neumann M, Rademakers R, Roeber S, Baker M, Kretschmar HA, Mackenzie IR. A new subtype of frontotemporal lobar degeneration with FUS pathology. *Brain* 2009;**132**(Pt 11):2922–31.
-
- 67.** Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, *et al.*

Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. *Acta Neuropathol* 2009;**117**(1):15–18.

68. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, *et al.* Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations. *Brain* 2012;**135**(Pt 3):693–708.

69. Roberson ED. Mouse models of frontotemporal dementia. *Ann Neurol* 2012;**72**(6):837–49.

70. Munoz DG, Woulfe J, Kertesz A. Argyrophilic thorny astrocyte clusters in association with Alzheimer's disease pathology in possible primary progressive aphasia. *Acta Neuropathol* 2007;**114**(4):347–57.

71. Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, Mann DM, *et al.* Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol* 2011;**122**(2):137–53.

72. Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, *et al.* Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain* 2011;**134**(Pt 9):2565–81.

73. Menon R, Baborie A, Jaros E, Mann DM, Ray PS, Lerner AJ. What's in a name? Neuronal intermediate filament inclusion disease (NIFID), frontotemporal lobar degeneration-intermediate filament (FTLD-IF) or frontotemporal lobar degeneration-fused in sarcoma (FTLD-FUS)? *J Neurol Neurosurg Psychiatry* 2011;**82**(12):1412–14.

74. Mackenzie IR, Foti D, Woulfe J, Hurwitz TA. Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions. *Brain* 2008;**131**(Pt 5):1282–93.

75. Lesage S, Le Ber I, Condroyer C, Broussolle E, Gabelle A, Thobois S, *et*

al. C9orf72 repeat expansions are a rare genetic cause of parkinsonism. Brain 2013;**136**(Pt 2):385–91.

76. Bozeat S, Gregory CA, Ralph MA, Hodges JR. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2000;**69**(2):178–86.

77. Harris JM, Gall C, Thompson JC, Richardson AM, Neary D, du Plessis D, *et al.* Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. *Neurology* 2013;**80**(20):1881–7.

78. Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, *et al.* Focal cortical presentations of Alzheimer's disease. *Brain* 2007;**130**(Pt 10):2636–45.

79. Chahal S, Rowe J. Dopamine transporter (dat) imaging can be normal with neuropathologically confirmed corticobasal degeneration. *J Neurol Neurosurg Psychiatry* 2013;**84**(11):e2.

80. Shelley BP, Hodges JR, Kipps CM, Xuereb JH, Bak TH. Is the pathology of corticobasal syndrome predictable in life? *Mov Disord* 2009;**24**(11):1593–9.

81. Mathew R, Bak TH, Hodges JR. Diagnostic criteria for corticobasal syndrome: a comparative study. *J Neurol Neurosurg Psychiatry* 2012;**83**(4):405–10.

82. Tang-Wai D, Lewis P, Boeve B, Hutton M, Golde T, Baker M, *et al.* Familial frontotemporal dementia associated with a novel presenilin-1 mutation. *Dement Geriatr Cogn Disord* 2002;**14**(1):13–21.

83. Halliday GM, Song YJ, Lepar G, Brooks WS, Kwok JB, Kersaitis C, *et al.* Pick bodies in a family with presenilin-1 Alzheimer's disease. *Ann Neurol* 2005;**57**(1):139–43.

84. Dermaut B, Kumar-Singh S, Engelborghs S, Theuns J, Rademakers R,

Saerens J, *et al.* A novel presenilin 1 mutation associated with Pick's disease but not beta-amyloid plaques. *Ann Neurol* 2004;**55**(5):617–26.

85. Irwin DJ, McMillan CT, Toledo JB, Arnold SE, Shaw LM, Wang LS, *et al.* Comparison of cerebrospinal fluid levels of tau and A β 1–42 in Alzheimer disease and frontotemporal degeneration using 2 analytical platforms. *Arch Neurol* 2012;**69**(8):1018–25.

86. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 2001;**103**(6):367–78.

87. Greene JD, Hodges JR, Ironside JW, Warlow CP. Progressive aphasia with rapidly progressive dementia in a 49 year old woman. *J Neurol Neurosurg Psychiatry* 1999;**66**(2):238–43.

88. Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, *et al.* Frontotemporal dementia: clinicopathological correlations. *Ann Neurol* 2006;**59**(6):952–62.

89. Mead S, Poulter M, Beck J, Webb TE, Campbell TA, Linehan JM, *et al.* Inherited prion disease with six octapeptide repeat insertional mutation – molecular analysis of phenotypic heterogeneity. *Brain* 2006;**129**(Pt 9):2297–317.

90. Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the 'bvFTD phenocopy syndrome'. *Curr Opin Neurol* 2010;**23**(6):628–32.

91. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol* 2011;**10**(2):162–72.

Section 2



Clinical phenotypes

Chapter 3

Overview of frontotemporal dementia and the variety of its clinical presentations



Matthew Jones and David Neary

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

Frontotemporal dementia (FTD) is the name given to a group of syndromes that are characterized by progressive atrophy of the frontal and temporal lobes of the brain. These neurodegenerative conditions are non-Alzheimer dementias and are linked by a range of pathologic processes collectively referred to as frontotemporal lobar degeneration (FTLD) spectrum pathology. The range of pathologic changes seen can broadly be split into three, according to the major protein seen deposited at post-mortem brain examination: tau, transactive response DNA-binding protein of 43 kDa (TDP-43), and the tumor-associated protein fused in sarcoma (FUS). Around a third of patients have a positive family history and the

heterogeneity of these conditions is further underlined by the range of genetic mutations now found in association with them. The commonest mutations seen are in the genes encoding progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), and chromosome 9 open reading frame 72 (*C9orf72*).

Whilst once considered a rare diagnosis that could not be made on clinical grounds in life, these syndromes are now recognized as being amongst the commoner forms of early-onset dementia. Three principle syndromic variants are described. The commonest is behavioral variant frontotemporal dementia (often abbreviated to simply FTD or bvFTD) and accounts for approximately half of the FTD spectrum cases seen. Then there are two presentations defined by disorders of language and/or conceptual function – semantic dementia (SD, also referred to as semantic variant primary progressive aphasia [PPA]) and progressive non-fluent aphasia (PNFA, also referred to as non-fluent variant primary progressive aphasia [nfvPPA]). Overlap with other neurodegenerative conditions is increasingly recognized; some patients with FTD may develop amyotrophic lateral sclerosis (ALS or motor neuron disease [MND]) or symptoms of a parkinsonian disorder. In particular there are close overlaps with corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). In this chapter we aim to offer an introduction to the clinical features of this heterogeneous group of conditions.

Epidemiology

Estimations of how common FTD is have varied greatly between research groups. Part of this may reflect genuine geographic variations in prevalence,

but some of the discrepancies are likely accounted for by differences in case ascertainment method and use of different diagnostic criteria.

In the Netherlands the overall prevalence was estimated at 1.1 per 100 000, although in the Zuid Holland region this rose to 2.7 per 100 000 [1]. In this study prevalence was calculated to be highest in the 60- to 69-year bracket at 9.4 per 100 000. In Northern Italy overall prevalence was found to be considerably higher at 17.6 per 100 000 [2]. In Southern Italy a door-to-door survey revealed a rate of FTD of 3.5% in all those over the age of 50 [3]. In Japan a number of outpatient clinic surveys have revealed rates of FTD to be between 6.8% and 12.7% amongst consecutive clinic patients with dementia [4]. In Cambridge (UK) the prevalence of FTD has been estimated at 15 per 100 000 in the 45- to 64-year-old age range [5]. A recent study from the USA calculated that the prevalence of FTD is 15–22 per 100 000 in 45- to 64-year-olds, which is broadly consistent with the Cambridge, UK estimation [6]. Based on those figures there are an estimated 20 000–300 000 people with FTD in the USA. Estimations on prevalence of FTD in developing countries are largely lacking [7].

FTD most commonly presents between the ages of 45 and 64, as indicated in the above studies. There is, however, a broad range of ages at which patients can present; experience from pathologic series in the UK indicates the age range for FTD presentation to be between 21 and 86 years [8, 9].

Classical features of frontotemporal dementia spectrum syndromes

Behavioral variant FTD (bvFTD)

Abnormalities in behavior are the hallmark of this disorder. It is the commonest of the FTD spectrum disorders and accounts for approximately half of all cases caused by FTLN pathology. Like all neurodegenerative conditions the symptoms start insidiously and gradually progress. Often initial behavioral symptoms are attributed to something else such as an affective disorder or stress. Changes in behavior may be subtle to begin with and a loss of interpersonal skills and altered conduct in social situations may be the first evidence of the condition clinically. The condition is associated with varying degrees of atrophy involving the frontal lobes, but anterior temporal atrophy is also often present.

Patients with bvFTD usually lack insight and thus do not seek medical attention for their symptoms. The next of kin or friends of the patient are usually responsible for bringing the situation to medical attention. Patients may lack social emotions such as sympathy and empathy. Patients lack the ability to infer the emotional feelings of others and may struggle to see other people's perspective. These deficits in social cognition and specifically theory of mind and empathy have become recognized as important aspects of bvFTD [10, 11]. These symptoms readily lead to lapses in normal social behavior that initially could be viewed as embarrassing, but as they progress may become increasingly hard to manage. Patients with bvFTD struggle to express emotion and may appear blunted in affect.

Significant phenotypic variation occurs in the behaviors seen in patients with bvFTD. Some patients present with overactivity and disinhibition, whereas others predominantly suffer from apathy and lack of drive. Whether disinhibited or apathetic, patients with bvFTD suffer from a loss of interest in their usual activities. Patients with bvFTD may manifest repetitive motor acts or verbal utterances. These may be simple stereotypies or sometimes more complex repetitive activities and phrases. Case studies

1 and 2 highlight some of the features of and differences between the disinhibited and apathetic presentations of bvFTD.

A change in eating behavior and dietary preferences is often seen in bvFTD. Patients may exhibit a preference for sweet foods, have food fads, or display gluttony. A tendency to overeat and stuff food into the mouth can be seen. Patients may place inedible objects into their mouth.

Patients with bvFTD may have altered responses to sensory stimuli. This can manifest as a lack of normal response to pain or, conversely, as an overreaction to innocuous stimuli [[12](#)].

In addition to altered behavior, psychiatric symptoms may be present in a minority of bvFTD cases. Some patients manifest delusional beliefs or suffer from hallucinations. Such psychiatric features are reported to occur more commonly in patients carrying a *C9orf72* hexanucleotide repeat expansion [[13](#)].

The behavioral features of bvFTD can be elicited by careful history taking from the patient, but often more critically, from a close relation of the patient. A structured approach to this is helpful so as not to overlook symptoms that patients and carers would otherwise fail to disclose spontaneously. A number of the behaviors described above can be embarrassing for carers to discuss and time spent with the informant away from the patient is usually necessary. Some of the described behaviors can be observed directly by the physician even in the relatively brief period of a standard outpatient consultation.

The cognitive features of bvFTD are usually those of a dysexecutive syndrome. These can be detected on neuropsychological testing. Patients may struggle with tasks requiring planning, problem-solving, mental flexibility, judgment, and attention. Other cognitive abilities such as language, visuospatial functioning, and memory, being more posterior cortical functions, are generally well preserved. However, patients with

bvFTD may appear to score badly on a range of cognitive measures and here the qualitative nature of their performance is of vital importance. Test performance is often overall characterized by inattention, difficulty changing set, impulsivity, and problems with impulse inhibition. Any of these problems may lead a patient to fail a given task, although not necessarily due to a deficit in the domain ostensibly being tested. For instance, poor memory test scores may be due to poor attention or a lack of spontaneous generation of response. In addition to testing the standard range of neuropsychological domains it is becoming increasingly common for tests of social cognition to be incorporated into bvFTD assessments.

Physical signs on neurologic examination are often absent at the time of presentation. Patients may have primitive reflexes such as grasp or snout reflexes and these may become more apparent as the illness progresses. Some patients have evidence of extrapyramidal signs in the form of rigidity and bradykinesia. A proportion of patients with bvFTD develop, or present with, evidence of ALS. Additional details on bvFTD are reviewed in .

Semantic dementia (SD)

This disorder, also known as semantic variant PPA in the latest classification system [14], is often initially characterized by a loss of memory for words. The condition is strongly associated with asymmetric atrophy of the anterior and inferior temporal lobes, usually left more than right.

Patients speak fluently but are relatively anomic with empty speech. Grammar and phonology are intact. In addition to the output problem, comprehension for words is affected, particularly for lower frequency or less familiar words. The disorder affects all aspects of semantic knowledge and thus patients have difficulty recognizing objects visually and identifying

sounds and smells (associative agnosia). None of these problems is due to an elementary perceptual deficit, but rather a breakdown in the semantic knowledge of what the object is.

Patients will often substitute more familiar, within category (coordinate), words for an item but progressively use more general terms or make superordinate category errors. This can be evident in spontaneous speech and is also detected on neuropsychological naming tests. When reading aloud patients may make regularization errors, pronouncing irregularly spelt words phonetically (*pint* said to sound like *hint*).

Failure to recognize objects can lead to misuse of household items or tools. Patients with SD may have significant difficulty in recognizing the faces (prosopagnosia) of those previously familiar to them. This particular feature has been linked to right-sided temporal atrophy [15]. Case studies 3 and 4 exemplify the features of patients with SD; Case 3 is typical of a patient with predominantly right temporal atrophy at presentation and Case 4 with predominantly left temporal atrophy.

Behavioral changes are common in SD [12], although patients tend to have a greater degree of insight than those with bvFTD. Some patients appear garrulous and can be hard to interrupt during spontaneous speech. Patients with SD may display an increased level of interest in a narrower range of activities. Many patients develop obsessions with word or number puzzles. Patients may clock watch and become obsessed with time and routine. Conversational themes become limited and repetitive. Similarly, food preference may become highly selective with dietary fads. Many of these behavioral changes can be conceptually linked to the loss of semantic knowledge; patients engage in an ever-narrowing range of behaviors and conversational topics, reflecting their loss of semantic meaning.

Physical examination is usually normal in SD. A small proportion of patients develop ALS. Further details on SD are reviewed in [Chapter 5](#).

Progressive non-fluent aphasia (PNFA)

This syndrome, known as nfvPPA in the latest classification system [14], is a disorder of language production and comprehension. The syndrome has been associated with atrophy in the left perisylvian region. In contrast to SD, which is a tightly defined clinical entity, there is much heterogeneity in what can be considered PNFA. At least part of the reason for this is that “non-fluency” can be caused by a number of different language problems. Consensus criteria in 1998 highlighted the importance of agrammatism, phonemic paraphasias, and anomia [16]. The 2011 classification system requires the presence of one or both of agrammatism and apraxia of speech (AOS). AOS refers to a problem with the planning of oral movements necessary for speech and, when present, results in effortful sounding speech distortions [17]. Patients with PNFA have a relative preservation of word meaning but can struggle to interpret syntactically complex sentences.

Other cognitive domains often remain remarkably intact and patients may function relatively independently early in the course of their illness. As the condition progresses speech becomes increasingly difficult, resulting in eventual mutism. Even at the stage of severely limited speech many patients continue to be able to communicate in writing although this too usually becomes affected.

Initially neurologic examination may be normal but in time some patients develop parkinsonism and/or limb apraxia. Signs of ALS may be seen in a minority.

In the 2011 PPA classification system a third aphasia syndrome is described: logopenic variant PPA. In this disorder patients exhibit word retrieval problems and struggle to repeat sentences and phrases. The features of semantic variant and non-fluent variant PPA are otherwise absent. This syndrome has more often been associated with underlying

Alzheimer's pathology [18] but as it is the most recently described of the progressive aphasia more data are needed regarding the accuracy with which this syndrome can predict underlying pathology. At this stage it cannot be considered as part of the FTD spectrum of disorders. Further details on these forms of PPA are reviewed in [Chapter 5](#).

Atypical presentations and the differential diagnosis of FTD

The diagnosis of FTD spectrum disorders rests upon a carefully taken history from the patient and caregiver and a full neurologic examination of the patient. Neuropsychological testing can be enormously helpful in delineating the cognitive basis for a clinical deficit and may also uncover unexpected deficiencies in other cognitive domains. Neuropsychology is especially helpful in the assessment of progressive aphasia syndromes. Structural and functional neuroimaging are important in helping to confirm the diagnosis as well as excluding other, non-neurodegenerative etiologies.

Differentiating FTD from Alzheimer's disease

In patients with an insidious onset and gradual progression to their symptoms the principle differential diagnosis to be made is from other neurodegenerative conditions. The disease that most often enters this differential diagnosis is Alzheimer's disease (AD). Whilst generally AD is a condition affecting older individuals there is considerable overlap in the range of ages of onset between AD and FTD, and AD has been found to be the commonest cause of early-onset dementia in a number of studies [19, 20]. AD is typically associated with deficits in episodic memory and a constellation of more posterior cortical deficits such as visuospatial and

constructional difficulties, however, considerable heterogeneity in the clinical presentation of AD is recognized [21, 22]. In a recent study of the accuracy of the 2011 FTD diagnostic criteria, the majority of cases that met FTD criteria, yet had alternative pathologies at post-mortem, were due to AD [23]. In several of these cases typical AD deficits of memory and visuospatial impairments were present on neuropsychological testing yet the patients met FTD criteria because of the presence of behavioral change and executive problems. The study did also highlight cases where patients may present with a circumscribed frontal lobe syndrome and even have frontal atrophy on structural imaging, yet have AD pathology at post-mortem. Indeed it is recognized that early-onset AD due to mutations in the presenilin 1 gene (*PSEN1*) may present with a FTD-like syndrome [24].

Whilst AD is known to masquerade clinically with a frontal lobe presentation, it is also recognized that some patients presenting with more typical AD symptoms can have FTLD spectrum pathology. In particular, amnesia has been reported to occur prominently in some patients with FTLD pathology [23, 25].

The recognition that AD is not clinically uniform is crucially important in accurately diagnosing early-onset dementias. Not only can AD occasionally present with frontal lobe symptoms, but it can also cause focal cognitive presentations characterized almost solely by visuospatial problems, language disturbance, or apraxia. In the case of these latter two situations this heterogeneity in AD presentation can cause further confusion in the diagnosis of FTD spectrum disorders. Several studies have highlighted that patients presenting with SD or PNFA may have underlying AD pathology [21, 26] and the accurate pathologic diagnosis of progressive aphasia syndromes in life remains challenging. The most recent classification system for PPA has been assessed to determine whether the clinical classification criteria predict underlying pathology [27]. In this

pathologically confirmed cohort study, patients meeting criteria for semantic variant PPA all had TDP-43 pathology. Seventy-five percent of patients meeting criteria for nfvPPA had FTLD spectrum pathologies (a mixture of tau-positive and TDP-43 types). Criteria for logopenic variant PPA were the least specific with patients exhibiting a broad range of pathologies, although AD was commonest. This would suggest that simply applying published criteria to patients with progressive language disorders might not be a sufficiently accurate way of predicting pathology. In a separate study of clinicopathologic correlation very high rates of diagnostic accuracy have been reported [28]. This study emphasized two overarching principles in achieving diagnostic success. First, patients with posterior cortical deficits and/or amnesia were likely to have AD and patients with anterior cortical symptoms of behavioral change were likely to have FTLD pathology. Second, patients in whom a striking specificity of neuropsychological deficit was observed (e.g., impaired semantics with preserved phonology and syntax) were more likely to have FTLD spectrum pathology. These studies serve to highlight that diagnostic criteria, whilst useful in standardizing research and clinical practice, are no substitute for the careful clinical assessment of experienced practitioners.

Because of these difficulties in symptom overlap between some cases of AD and FTD the differential diagnosis will always be challenging on clinical grounds alone in certain patients. Patterns of regional atrophy on structural imaging may also overlap, so more specific biomarker technology may be of assistance. The advent of amyloid positron emission tomography (PET) imaging and improvements in cerebrospinal fluid (CSF) biomarker analysis should help to make the ante-mortem distinction between AD and FTLD pathologies easier.

Differentiating FTD from other neurodegenerative conditions

Although AD is the neurodegenerative condition that most commonly mimics FTD spectrum disorders, there can be occasions where other diseases enter the differential diagnosis. One such example is dementia with Lewy bodies (DLB). Generally the presence of more posterior cortical deficits, fluctuations, parkinsonism, and hallucinations make this diagnosis straightforward. However, as previously discussed, parkinsonism may occur in a subset of patients with FTD and some patients also have delusions and hallucinations. Additionally, the tangential line of thought seen in DLB can appear similar to the unmonitored output of some patients with FTD. In a study of FTD diagnostic criteria accuracy some patients met FTD criteria yet had DLB or mixed DLB and AD pathology [29]. Previous reports have suggested that a subgroup of FTD patients may mimic DLB [30] and that small numbers of patients with clinical DLB have mutations in *C9orf72* and could be atypical FTD cases [31].

Occasionally patients presenting with a disorder compatible with FTD or progressive aphasia may be ultimately found to have prion pathology [23, 27, 31, 32] but typically the rapid progression of dementia and development of other neurologic symptoms makes this diagnosis relatively easy.

Differentiation from cerebrovascular disease

Vascular dementia (VaD) is a common cause of cognitive impairment and diagnostic criteria emphasize the importance of deficits in multiple cognitive domains, abnormal findings on neurologic examination, and vascular findings on neuroimaging [33]. The presence of vascular risk factors is also important. The advent of readily available magnetic resonance imaging (MRI) has undoubtedly made the diagnosis easier. However, alterations in behavior are known to occur in VaD and may make differentiation from FTD difficult. Accordingly, some patients that meet

diagnostic criteria for FTD may have vascular pathology at autopsy [23]. Specific behavioral features that have been found to help differentiate FTD from VaD include loss of basic emotions, food cramming, pacing a fixed routine, and the absence of insightfulness [34]. However, that is not to say that these features cannot be seen in VaD, albeit with less frequency. Other work has highlighted cognitive differences between the two syndromes with FTD patients performing better on digit span and constructional tasks [35].

Differentiation from psychiatric conditions

As can be seen from the description of some of the symptoms in FTD there is significant overlap between certain features of this neurodegenerative disease and some psychiatric conditions. The apathy of FTD can be mistaken for the low mood of depression. Similarly, the altered emotional reactivity seen in FTD can be confused with the symptoms of an affective disorder. Hallucinations and delusions are first-rank symptoms of schizophrenia and can also occur in some FTD patients. Patients with psychiatric disorders may score poorly on neuropsychological testing so the qualitative interpretation of how they perform is important.

Patients with FTD are much more likely than those with other neurodegenerative diseases to have received a prior diagnosis of a psychiatric disorder, most commonly depression or bipolar affective disorder, but also occasionally schizophrenia [36]. There are, however, important differences in behavior between patients with FTD and those with psychiatric conditions. In FTD it is unusual for patients to complain of subjective sadness, unlike in depression. Patients with FTD are unlikely to show remorse for their abnormal behavior whereas patients with mania generally do. FTD patients are less likely to have insight. In healthcare consultations the spontaneous behavior of FTD patients has been found to

differ from that of patients with psychiatric conditions: Verbal or physical interruption of the consultation occurred more often in patients with SD and a lack of concern for the clinicians expectations was more common in FTD patients [37].

The nature of the clinical course of a behavioral syndrome can also help differentiate the neurodegenerative etiologies from the psychiatric. In general those patients with neurodegeneration will have a typical insidious onset and gradual but relentless progression. In addition, patients with neurodegenerative disease should have atrophy on brain imaging either at presentation or on follow-up. However, these general rules have been called into question by the identification of patients fulfilling diagnostic criteria for FTD at initial presentation but then either very slowly progressing or failing to progress at all [38–40]. These patients are described as being different to progressive FTD patients by having little or no atrophy on MRI and performing better on neuropsychological tasks and measures of activities of daily living. There is a striking male predominance. The status of such patients remains unclear and they are sometimes referred to as FTD “phenocopies.” They may represent a group with no neurodegenerative disease at all and the possibility of the symptoms being due to an Asperger spectrum-type condition has been raised [38]. However, there are also reports of some such patients genuinely progressing, albeit very slowly, and showing evidence of FTLD pathology at autopsy [41]. Intriguingly there are now reports of some slowly progressive FTD patients being positive for the *C9orf72* mutation [42], suggesting this may be a potential cause of the slowly progressive phenotype.

The association of psychotic symptoms with the *C9orf72* mutation merits specific attention. In one study characterizing the clinical phenotype of *C9orf72* mutation carriers, psychosis was present in 38% of individuals

versus < 4% of non-mutation carriers [13]. These patients had all initially received a psychiatric diagnosis prior to referral to the neurology clinic. Many of the patients had florid, mono-delusional psychosis and bizarre irrational behavior. Case study 5 describes one such patient as an example. Other studies have also uncovered high rates of psychotic features in patients with *C9orf72* mutations [43, 44]. Thus the presence of late-onset psychosis, particularly if characterized by florid mono-delusional beliefs and irrational behavior, should prompt consideration of neurologic referral.

Because of the obvious difficulties in diagnosing this spectrum of disorders we have developed a highly structured approach in our own clinic to maintain high rates of diagnostic accuracy. We use a semi-structured neurologic history tool to extract uniform clinical information and all patients have full neurologic examination. Where possible the neuropsychologist joins the neurologist for this process before taking the patient away for a standardized neuropsychological test battery. This also gives the neurologist time with the caregivers to further discuss behavioral aspects that many relatives prefer not to speak about in front of the patient. Following structural neuroimaging all cases are discussed in a multidisciplinary meeting to reach a consensus diagnosis. Once this process is complete the patient and caregivers are invited back to discuss the results in a separate appointment.

Clinical course

As a neurodegenerative disease, FTD inevitably results in progressively worse cognitive impairment with time. Although patients present initially with behavioral and cognitive symptoms, neurologic symptoms and signs become increasingly prevalent as the disease progresses. Disorders of gait

and reduced mobility should be anticipated. Communication reduces with time in all forms of FTD, albeit for different underlying reasons. Many patients develop swallowing difficulties and become prone to choking. In some patients limb apraxia can become disabling. Patients with FTD may become incontinent of urine and feces and appear unconcerned by this.

Despite the fact that the condition progresses in general not all behavioral features worsen over time. For instance, patients in whom disinhibited behavior is prominent at presentation often become progressively more apathetic over time. The overeating that can characterize the dietary disturbance in many patients often evolves eventually into a gradual reduction of oral intake. Because of disease progression the majority of patients will eventually require some form of institutional care.

Because FTD is a heterogeneous condition the clinical course and prognosis varies greatly between patients. Survival has been assessed in a number of studies but comparison between studies is hindered by differing use of diagnostic criteria, the degree of autopsy verification of diagnosis, and inclusion of different clinical phenotypes.

In one large series of patients, survival rates in FTD were not seen to differ from those in AD. The mean duration of illness was 8.3 \pm 2.7 years [45]. Other studies have suggested that FTD progresses to death faster than AD [46]. In one study median survival of patients with FTD was 6 \pm 1.1 years for FTD alone and 3 \pm 0.4 years for FTD with MND. A subset of patients with tau pathology had a longer median survival time of 9 \pm 0.9 years [47]. However, in a pathologically proven cohort from the USA where MND cases were excluded, tau-positive cases had a poorer survival rate [48]. Overall median survival from symptom onset was 6.7 years. In Germany median survival from symptom onset in FTD spectrum disorders (excluding MND cases) was 11.8 years [49]. This study found longer

survival in SD, shortest in bvFTD, and survival in PNFA to be intermediate between the two. The commonest cause of death was a respiratory disorder (27%, mostly pneumonia and choking on food) followed by a circulatory system disorder (19%), followed by cachexia (14%). The most consistent finding across studies is that unsurprisingly the presence of clinical MND shortens survival. Unresolved issues surrounding the status of slow-progressing or “phenocopy” FTD cases makes prediction of survival and overall prognosis very difficult at the time of diagnosis, unless neurologic signs of MND are present.

Managing FTD

The management of FTD poses a unique set of problems. The majority of patients diagnosed with this spectrum of dementias is of working age and may have dependents such as children still in full-time education. The early loss of insight and altered behavior of patients puts great strain on family and social relationships. Some patients are diagnosed with FTD only having already been diagnosed with and treated for a psychiatric condition. Compounding all of this is the fact that general awareness and understanding of FTD is low amongst primary care physicians and some mental health clinicians to whom the patient and family are likely to initially present. This means that by the time a patient and their family reach the point of diagnosis in a specialist dementia or neurology clinic they can already feel short-changed by the healthcare system they have been through to that point. Recognizing this is crucial and management of FTD is about trying to help the caregivers as well as the patients. In our clinic we use a separate appointment, after completion of the clinical and radiologic assessment, to break the news of the diagnosis. This usually involves explanation of the

condition and its symptoms, addressing the issue of heritability where appropriate, discussion of prognosis, and time spent with a specialist social worker to address practical and financial concerns.

Caregivers

FTD has a devastating effect not only on the patient but also on members of the family who typically become caregivers. Those looking after and living with patients with FTD are under a greater degree of burden than those caring for patients with other dementias such as AD [[50](#), [51](#)]. Rates of depression are higher in caregivers of FTD patients compared with those of AD patients [[52](#)]. The apathy, behavioral changes, and loss of insight of FTD patients has been found to particularly affect carers [[53](#), [54](#)]. Unsurprisingly the severity of a patient's FTD symptoms was found to correlate positively with measures of caregiver burden and negatively with their mental health. Caregivers report valuing the support and information they receive from healthcare workers who are knowledgeable about the condition. Informing and educating caregivers about the nature of the patient's disease and helping them to understand the symptoms is a critical step in managing the condition.

In our own clinic we have found the early involvement of a specialist social worker to be of value to carers. This helps to address some of the very real practical issues that inevitably occur. Families need advice on how to access the most appropriate community support and financial assistance or benefits where available. Time needs to be given for planning periods of respite care and eventually to planning the transition of the patient to institutional care. We find that providing written information on the patient's condition to be valuable; caregivers can then share this information with other family members, friends, or their primary healthcare

physicians. Support groups can offer another valuable source of help to caregivers, particularly if a disease-specific support group can be located.

Given the strong genetic influence in FTD a patient's family may have worries and questions regarding heritability of the disease. It is therefore crucial to have close links with an experienced clinical genetics department to help facilitate appropriate genetic counseling.

Patients

Currently there are no therapeutic interventions proven to alter the disease progression in any FTD spectrum disorder. Management therefore tends to revolve around attempting to control or deal with patients' symptoms by environmental modification, pharmacologic treatments, and caregiver education.

There are currently no licensed medications even for symptomatic control in FTD. Despite this, rates of "off-label" medication use in FTD are reported to be high. One study in the USA found that use of Food and Drug Administration (FDA)-approved AD drugs was as common in FTD as in AD [55]. Over 40% of FTD patients had been prescribed a cholinesterase inhibitor, almost 30% memantine, and 43% an antidepressant.

A number of drugs have been subject to mostly small-scale studies in FTD. The rationale for trying most of these therapies has been the evidence that some brain neurotransmitter systems are altered in FTD. The data on the serotonergic system overall support serotonin deficiency in FTD [56]. Accordingly, a number of studies of antidepressants that boost serotonin levels have been undertaken; most are small, uncontrolled, and of short duration. A meta-analysis of the results indicated an improvement in scores on a neuropsychiatric outcome measure [56]. This accords with many physicians' anecdotal experience that selective serotonin reuptake inhibitors

(SSRIs) can be modestly beneficial in FTD. However, the first randomized, double-blinded, placebo-controlled study (using paroxetine) showed no beneficial effect and suggested a possible worsening of cognition in the study drug group [57]. One possible explanation comes from a post-mortem neurochemical study of FTD, AD, and control brains [58]. This work suggested that the changes seen in FTD brains could lead to an excess of extraneural serotonin (5-HT), so perhaps therapy with a 5-HT_{1A} receptor antagonist would be more beneficial. Trazadone, a serotonergic agent with a different mechanism to SSRIs, demonstrated an improvement in behavior in a randomized, double-blinded, placebo-controlled study of FTD [59].

Although there is little evidence of cholinergic disturbance in FTD [56] cholinesterase inhibitors have been trialled as a treatment for FTD. Galantamine failed to show a beneficial effect in a group of patients with bvFTD and PPA [60].

There are no high-quality trials of antipsychotic drugs in FTD but they are sometimes prescribed on the basis of their known beneficial effects on symptoms such as agitation, hallucination, and delusions in other conditions. Patients with FTD may have parkinsonism as part of their clinical syndrome and neuroimaging supports dysfunction of the dopaminergic system [61]. It is perhaps unsurprising therefore that, when used in FTD, dopamine-blocking antipsychotic drugs carry a high risk of extrapyramidal side effects [62].

Memantine, a recently approved drug for use in AD, has been subject to investigation in FTD. Initial open label studies suggested the drug to be well tolerated [63, 64] but a randomized, double-blinded, placebo-controlled study in 81 FTD patients showed no beneficial effect of the drug [65].

On the basis that oxytocin may improve performance on social cognition tasks in healthy adults [66] intranasal administration has been

tested in patients with FTD, yielding positive short-term benefits in behavior, although further studies need to be carried out [67].

Few data exist on the best non-pharmacologic interventions for patients with FTD. Education of the caregivers is important to help them understand and manage the patient's behavior day to day. At least in the early stages the involvement of speech and language specialists, occupational therapists, and neuro-rehabilitation has been recommended [68].

The future

Given the recent advances in the understanding of the pathology and genetics of FTD, there is much hope that the future will hold the prospect of molecular-specific therapies with the eventual aim of disease-modifying treatments. The relatively high rate of familial disease allows the possibility of identifying presymptomatic or very early-stage gene carriers in whom pathology can be predicted. Such individuals may be an ideal group for studies of potential disease-modifying treatments. In the meantime further progress must be made in the fields of molecular-specific biomarkers and early clinical symptom recognition to capitalize on potential new treatments as they hopefully emerge.

Case studies

Case 1: Disinhibited FTD

A previously well 55-year-old man was referred to the neurology clinic following a two-year history of progressive behavioral change. He had developed childish jocularity at work and his foolish jokes in the workplace had led to accidents. He behaved in a

disinhibited manner in public with no regard for the effects his behavior had on others. He was initially seen in the psychiatry services where no psychiatric explanation for his condition could be found.

In the neurology clinic he appeared unconcerned with a fatuous affect. He joked excessively and used repetitive phrases. He made inappropriate, uncaring remarks about other patients. He had no significant past medical history or family history. Neurologic examination revealed generally brisk deep tendon reflexes and an upgoing right plantar response.

Neuropsychological assessment revealed him to be orientated and able to recall recent events. Speech was linguistically and grammatically correct but unmonitored and frequently off the point. Comprehension was normal save for concrete interpretation of metaphor and proverb. Reading and writing were unaffected. Verbal fluency was reduced. Visuospatial function was preserved, as was praxis. Memory testing revealed poor open-ended recall. Tests of executive function were performed well overall although some perseverative errors were noted. His overall performance was characterized by quick, impulsive responses and a lack of checking.

His condition slowly progressed over the next 10 years. He gradually became more apathetic with less spontaneous speech and a tendency for increasing use of stereotyped phrases. He became more routine bound. Serial neuropsychological testing revealed the preservation of visuospatial skills, reading, and writing. However, performance on memory and executive tests worsened. Physically he remained generally well with only the development of grasp reflexes on neurologic examination.

He died 12 years after symptoms onset from a cardiac arrest. Post-mortem examination revealed TDP-43 (type B) pathology.

Case 2: Apathetic FTD

A 53-year-old woman was referred to the neurology clinic from psychiatry services. She had become progressively more apathetic over the preceding two years. She neglected her usual day-to-day activities such as housework and shopping. She lost interest in her occupation and paid little attention to her physical appearance. She developed urinary incontinence about which she was unconcerned.

When asked about her symptoms she ascribed them to “not being bothered.” She did not endorse feelings of low mood or anxiety. She did not have a change in her sleep pattern or diet and her weight was stable. Neurologic examination revealed a positive jaw jerk, snout reflex, and upgoing plantar responses. Neuropsychological assessment revealed her to have a bland affect and her test performance was characterized by marked impersistence of effort and economical responses. She was fully orientated in time and place. In language, naming and comprehension were normal, her understanding of grammar was intact. Reading was normal and whilst her writing showed a preserved script and normal spelling there was marked perseveration in what she wrote. Verbal fluency was reduced. Visuospatial function was intact. Her memory was inefficient and she required prompts to recall information accurately.

During follow-up she progressively deteriorated. She became profoundly apathetic, preferring to stay in bed. She developed a

tendency to overeat sweet foods and would actively seek such foods out. Following a period of weight gain she lost interest in food and subsequently lost weight. However, at this stage she would attempt to put inedible objects into her mouth. Her speech became echolalic or limited to a few stereotyped phrases and this eventually progressed to mutism. During this deterioration it was possible to demonstrate that she could visually locate and identify objects and faces correctly. She showed no evidence of spatial disorientation.

She died of a respiratory tract infection seven years after symptom onset. Post-mortem examination revealed tau (Pick-type) pathology.

Case 3: Semantic dementia (right temporal lobe predominant)

A 68-year-old man presented with mild word-finding difficulties and a problem recognizing faces. He had become obsessional and prone to clock watching. He particularly favored watching certain quiz shows on television. He had become less caring toward his wife. He complained of an altered awareness of temperature when testing water with his hands. There was no past medical history and no family history of note. Neurologic examination was normal.

Neuropsychological testing found him to be rapid, impulsive, and garrulous. His spontaneous speech contained no frank word errors although there was a tendency for him to return to the same themes. He was able to identify even low-frequency words (microphone, magnifying glass) from description. By contrast he was unable to name objects accurately from line drawings. He could understand sentences and repeat words and phrases normally.

Interpretation of metaphor and proverb was rather literal. He read words without regularization errors and could write without spelling errors. He was unable to recognize famous faces or monuments. Tasks of visual construction were performed well, as were tasks of praxis. Memory tests revealed low scores on delayed recall although he was well orientated and able to give an accurate autobiographical account and describe recent news events. He passed all tests of executive function except those where an understanding of pictures was needed.

MRI and single photon emission tomography (SPECT) imaging demonstrated right-greater-than-left temporal atrophy and hypoperfusion, respectively.

As his condition progressed, more complex repetitive behavior developed – he would periodically walk to the kitchen and wail, bemoaning the death of relatives with stereotyped phrases. He became more preoccupied with time and quiz shows. He showed an exaggerated response to innocuous tactile stimuli.

His performance on picture-naming tasks worsened and there was a discrepancy between his very poor performance on pictures of living things and his relatively better performance for inanimate items.

After three years of follow-up he had to stop attending clinic and was admitted to a care home. He had slowed down physically and produced little spontaneous speech. He continued to display repetitive behaviors, such as repeatedly checking locks on doors and non-verbal vocalizations. Neurologic examination remained normal.

Case 4: Semantic dementia (left temporal lobe predominant)

A 63-year-old man was referred to the clinic because of difficulties finding the right word for things. He had been aware of problems gradually worsening over the last five years. He particularly struggled to name animals and vegetables. He did not always understand low-frequency words. He had started to read less but still wrote fluently. He was able to recognize faces and objects. He never became lost and could drive without difficulty. There were no behavioral changes or alterations in diet. There was no significant family history and neurologic examination was normal. SPECT scanning showed reduced perfusion of predominantly the left temporal lobe and MRI revealed atrophy of the left anterior temporal pole.

Neuropsychological testing revealed a principal problem of anomia. He was able to produce a reasonable amount of semantic information about objects but this information tended to be personally relevant. Word comprehension was impaired for low-frequency words only. Episodic memory and digit span were normal. Calculation was very good. Tasks of a visual perceptual and spatial nature were completed well.

Over the following years his naming deteriorated and he developed symptoms of poor face recognition for less familiar acquaintances. He became rather irritable and progressively more bound by performing certain activities at specific times. He became obsessed by quiz shows. Neurologic examination remained normal. Repeat neuropsychology demonstrated progressive worsening of naming and a gradual deterioration in visual recognition of objects and faces. Digit span and calculation were well preserved.

Six years after presentation his comprehension of speech had deteriorated and he no longer enjoyed watching television because of this. He stopped reading but was obsessed by word search puzzles. Face and object recognition deteriorated further. He remained physically well but had to stop driving because of his symptoms; he had little insight into these potential dangers and obsessed about the loss of his license. He stopped attending clinic after moving out of the area.

Case 5: FTD with psychosis (*C9orf72*)

A 71-year-old lady was referred to the neurology clinic with a four-year history of wanting to stay in bed. A complete change in personality was described by her husband who felt she now lived in a world of her own, largely within the confines of her bed. The patient attributed her symptoms to an old leg injury and felt that lying in bed allowed her nerves to heal. She complained of pain in her legs and pelvic region. She claimed to have a special understanding of how the nervous system worked. She described seeing the devil in various forms and had spoken out loudly about this when she was taken to church. She described hearing the voice of her husband when he was not present. Her husband described her as being overly affectionate and prone to hugging and kissing strangers. She became incontinent of urine and was unconcerned by this. There was a strong family history with one sister having died of MND and a brother diagnosed with FTD. Neurologic examination revealed palmomental reflexes, brisk deep tendon reflexes, and fasciculations in the arms. Her left arm was weak.

A CT scan of the brain showed mild frontotemporal atrophy. Neuropsychological testing found her to be impulsive, concrete in her thinking, and to have poor attention.

She rapidly developed dysarthria and dysphagia with clinical signs of bulbar and pseudobulbar palsy. She developed a tendency to cram food into her mouth that exacerbated her swallowing problems. Her limbs became progressively weaker and she developed anarthria. She remained able to write simple sentences to communicate. She died of MND less than 18 months after her first presentation to the neurology clinic.

References

1. Rosso S, Donker Kaat L, Baks T, Joosse M, de Koning I, Pijnenburg Y, de Jong D, Dooijes D, Kamphorst W, Ravid R *et al.* Frontotemporal dementia in the Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain* 2003;**126**(Pt 9):2016–2022.
2. Borroni B, Alberici A, Grassi M, Turla M, Zanetti O, Bianchetti A, Dalla Volta G, Rozzini R, Gilberti N, Bellelli G *et al.* Is frontotemporal lobar degeneration a rare disorder? Evidence from a preliminary study in Brescia county, Italy. *J Alzheimers Dis* 2010;**19**(1):111–116. doi: 110.3233/JAD-2010–1208.
3. Bernardi L, Frangipane F, Smirne N, Colao R, Puccio G, Curcio SA, Mirabelli M, Maletta R, Anfossi M, Gallo M *et al.* Epidemiology and genetics of frontotemporal dementia: a door-to-door survey in southern Italy. *Neurobiol Aging* 2012;**33**(12):2948.e1–2948.e10.
4. Ikeda M, Ishikawa T, Tanabe H. Epidemiology of frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* 2004;**17**(4):265–268.

-
5. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology* 2002;**58**(11):1615–1621.
-
6. Knopman DS, Roberts RO. Estimating the number of persons with frontotemporal lobar degeneration in the US population. *J Mol Neurosci* 2011;**45**(3):330–335.
-
7. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. *Int Rev Psychiatry* 2013;**25**(2):130–137.
-
8. Snowden JS, Neary D, Mann DM. Autopsy proven sporadic frontotemporal dementia due to microvacuolar-type histology, with onset at 21 years of age. *J Neurol Neurosurg Psychiatry* 2004;**75**(9):1337–1339.
-
9. Baborie A, Griffiths TD, Jaros E, McKeith IG, Burn DJ, Richardson A, Ferrari R, Moreno J, Momeni P, Duplessis D *et al.* Pathological correlates of frontotemporal lobar degeneration in the elderly. *Acta Neuropathol* 2011;**121**(3):365–371.
-
10. Kipps CM, Hodges JR. Theory of mind in frontotemporal dementia. *Soc Neurosci* 2006;**1**(3–4):235–244.
-
11. Adenzato M, Cavallo M, Enrici I. Theory of mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels. *Neuropsychologia* 2010;**48**(1):2–12.
-
12. Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* 2001;**70**(3):323–332.
-
13. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, Jones M, Gerhard A, Davidson YS, Robinson A *et al.* Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations. *Brain* 2012;**135**(Pt 3):693–708.

-
- 14.** Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF *et al.* Classification of primary progressive aphasia and its variants. *Neurology* 2011;**76**(11):1006–1014.
-
- 15.** Snowden JS, Thompson JC, Neary D. Knowledge of famous faces and names in semantic dementia. *Brain* 2004;**127**(Pt 4):860–872.
-
- 16.** Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;**51**(6):1546–1554.
-
- 17.** Josephs KA, Duffy JR, Strand EA, Whitwell JL, Layton KF, Parisi JE, Hauser MF, Witte RJ, Boeve BF, Knopman DS *et al.* Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain* 2006;**129**(Pt 6):1385–1398.
-
- 18.** Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, Perani D, Garibotto V, Cappa SF, Miller BL. The logopenic/phonological variant of primary progressive aphasia. *Neurology* 2008;**71**(16):1227–1234.
-
- 19.** Mercy L, Hodges JR, Dawson K, Barker RA, Brayne C. Incidence of early-onset dementias in Cambridgeshire, United Kingdom. *Neurology* 2008;**71**(19):1496–1499.
-
- 20.** Garre-Olmo J, Genis Batlle D, del Mar Fernandez M, Marquez Daniel F, de Eugenio Huelamo R, Casadevall T, Turbau Recio J, Turon Estrada A, Lopez-Pousa S. Incidence and subtypes of early-onset dementia in a geographically defined general population. *Neurology* 2010;**75**(14):1249–1255.
-
- 21.** Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR. Focal cortical presentations of Alzheimer's disease. *Brain* 2007;**130**(10):2636–2645.

-
- 22.** Stopford CL, Snowden JS, Thompson JC, Neary D. Variability in cognitive presentation of Alzheimer's disease. *Cortex* 2008;**44**(2):185–195.
-
- 23.** Harris JM, Gall C, Thompson JC, Richardson AM, Neary D, du Plessis D, Pal P, Mann DM, Snowden JS, Jones M. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. *Neurology* 2013;**80**(20):1881–1887.
-
- 24.** Mendez MF, McMurtray A. Frontotemporal dementia-like phenotypes associated with presenilin-1 mutations. *Am J Alzheimers Dis Other Demen* 2006;**21**(4):281–286.
-
- 25.** Graham A, Davies R, Xuereb J, Halliday G, Kril J, Creasey H, Graham K, Hodges J. Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* 2005;**128**(Pt 3):597–605.
-
- 26.** Knibb J, Xuereb J, Patterson K, Hodges J. Clinical and pathological characterization of progressive aphasia. *Ann Neurol* 2006;**59**(1):156–165.
-
- 27.** Harris JM, Gall C, Thompson JC, Richardson AM, Neary D, du Plessis D, Pal P, Mann DM, Snowden JS, Jones M. Classification and pathology of primary progressive aphasia. *Neurology* 2013;**81**(21):1832–1837.
-
- 28.** Snowden J, Thompson J, Stopford C, Richardson A, Gerhard A, Neary D, Mann D. The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships. *Brain* 2011;**134**(Pt 9):2478–2492.
-
- 29.** Harris J, Gall C, Thompson J, Richardson A, Neary D, du Plessis D, Pal P, Mann D, Snowden J, Jones M. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. *Neurology* 2013;**80**(20):1881–1887.
-
- 30.** Claassen DO, Parisi JE, Giannini C, Boeve BF, Dickson DW, Josephs KA. Frontotemporal dementia mimicking dementia with Lewy bodies. *Cogn Behav Neurol* 2008;**21**(3):157–163.
-

31. Snowden JS, Rollinson S, Lafon C, Harris J, Thompson J, Richardson AM, Jones M, Gerhard A, Neary D, Mann DM *et al.* Psychosis, *C9ORF72* and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* 2012;**83**(10):1031–1032.

32. Kobylecki C, Thompson JC, Jones M, Mills SJ, Shaunak S, Ironside JW, Snowden JS, Richardson AM. Sporadic Creutzfeldt-Jakob disease presenting as progressive nonfluent aphasia with speech apraxia. *Alzheimer Dis Assoc Disord* 2013;**27**(4):384–386.

33. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A *et al.* Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;**43**(2):250–260.

34. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 2001;**103**(6):367–378.

35. Cherrier MM, Mendez MF, Perryman KM, Pachana NA, Miller BL, Cummings JL. Frontotemporal dementia versus vascular dementia: differential features on mental status examination. *J Am Geriatr Soc* 1997;**45**(5):579–583.

36. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry* 2011;**72**(2):126–133.

37. Rankin KP, Santos-Modesitt W, Kramer JH, Pavlic D, Beckman V, Miller BL. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry* 2008;**69**(1):60–73.

38. Hornberger M, Shelley BP, Kipps CM, Piguet O, Hodges JR. Can progressive and non-progressive behavioural variant frontotemporal dementia be

distinguished at presentation? *J Neurol Neurosurg Psychiatry* 2009;**80**(6):591–593.

39. Kipps CM, Davies RR, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Clinical significance of lobar atrophy in frontotemporal dementia: application of an MRI visual rating scale. *Dement Geriatr Cogn Disord* 2007;**23**(5):334–342.

40. Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol* 2006;**63**(11):1627–1631.

41. Brodtmann A, Cowie T, McLean C, Darby D. Phenocopy or variant: a longitudinal study of very slowly progressive frontotemporal dementia. *BMJ Case Rep* 2013;2013.

42. Khan BK, Yokoyama JS, Takada LT, Sha SJ, Rutherford NJ, Fong JC, Karydas AM, Wu T, Ketelle RS, Baker MC *et al.* Atypical, slowly progressive behavioural variant frontotemporal dementia associated with *C9ORF72* hexanucleotide expansion. *J Neurol Neurosurg Psychiatry* 2012;**83**(4):358–364.

43. Kertesz A, Ang LC, Jesso S, MacKinley J, Baker M, Brown P, Shoesmith C, Rademakers R, Finger EC. Psychosis and hallucinations in frontotemporal dementia with the *C9ORF72* mutation: a detailed clinical cohort. *Cogn Behav Neurol* 2013;**26**(3):146–154.

44. Dobson-Stone C, Hallupp M, Bartley L, Shepherd CE, Halliday GM, Schofield PR, Hodges JR, Kwok JB. *C9ORF72* repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. *Neurology* 2012;**79**(10):995–1001.

45. Pasquier F, Richard F, Lebert F. Natural history of frontotemporal dementia: comparison with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2004;**17**(4):253–257.

46. Roberson ED, Hesse JH, Rose KD, Slama H, Johnson JK, Yaffe K, Forman

MS, Miller CA, Trojanowski JQ, Kramer JH *et al*. Frontotemporal dementia progresses to death faster than Alzheimer disease. *Neurology* 2005;**65**(5):719–725.

47. Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. *Neurology* 2003;**61**(3):349–354.

48. Xie SX, Forman MS, Farmer J, Moore P, Wang Y, Wang X, Clark CM, Coslett HB, Chatterjee A, Arnold SE *et al*. Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2008;**79**(2):126–129.

49. Nunnemann S, Last D, Schuster T, Forstl H, Kurz A, Diehl-Schmid J. Survival in a German population with frontotemporal lobar degeneration. *Neuroepidemiol-ogy* 2011;**37**(3–4):160–165.

50. Mioshi E, Foxe D, Leslie F, Savage S, Hsieh S, Miller L, Hodges JR, Piguet O. The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2013;**27**(1):68–73.

51. de Vugt ME, Riedijk SR, Aalten P, Tibben A, van Swieten JC, Verhey FR. Impact of behavioural problems on spousal caregivers: a comparison between Alzheimer's disease and frontotemporal dementia. *Dement Geriatr Cogn Disord* 2006;**22**(1):35–41.

52. Mioshi E, Bristow M, Cook R, Hodges JR. Factors underlying caregiver stress in frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2009;**27**(1):76–81.

53. Diehl-Schmid J, Schmidt EM, Nunnemann S, Riedl L, Kurz A, Forstl H, Wagenpfeil S, Cramer B. Caregiver burden and needs in frontotemporal dementia. *J Geriatr Psychiatry Neurol* 2013;**26**(4):221–229.

54. Wong CC, Wallhagen MI. Frontotemporal dementia: the impact of patient behavioral symptoms on the physical and mental health of family caregivers.

Dement Geriatr Cogn Dis Extra 2012;**2**(1):516–528.

55. Bei H, Ross L, Neuhaus J, Knopman D, Kramer J, Boeve B, Caselli RJ, Graff-Radford N, Mendez MF, Miller BL *et al.* Off-label medication use in frontotemporal dementia. *Am J Alzheimers Dis Other Dement* 2010;**25**(2):128–133.

56. Huey ED, Putnam KT, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* 2006;**66**(1):17–22.

57. Deakin JB, Rahman S, Nestor PJ, Hodges JR, Sahakian BJ. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial. *Psychopharmacology (Berl)* 2004;**172**(4):400–408.

58. Bowen DM, Procter AW, Mann DM, Snowden JS, Esiri MM, Neary D, Francis PT. Imbalance of a serotonergic system in frontotemporal dementia: implication for pharmacotherapy. *Psychopharmacology (Berl)* 2008;**196**(4):603–610.

59. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. *Dement Geriatr Cogn Disord* 2004;**17**(4):355–359.

60. Kertesz A, Morlog D, Light M, Blair M, Davidson W, Jesso S, Brashear R. Galantamine in frontotemporal dementia and primary progressive aphasia. *Dement Geriatr Cogn Disord* 2008;**25**(2):178–185.

61. Rinne JO, Laine M, Kaasinen V, Norvasuo-Heila MK, Nagren K, Helenius H. Striatal dopamine transporter and extrapyramidal symptoms in frontotemporal dementia. *Neurology* 2002;**58**(10):1489–1493.

62. Pijnenburg YA, Sampson EL, Harvey RJ, Fox NC, Rossor MN. Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. *Int J Geriatr Psychiatry* 2003;**18**(1):67–72.

-
- 63.** Boxer AL, Lipton AM, Womack K, Merrilees J, Neuhaus J, Pavlic D, Gandhi A, Red D, Martin-Cook K, Svetlik D *et al.* An open-label study of memantine treatment in 3 subtypes of frontotemporal lobar degeneration. *Alzheimer Dis Assoc Disord* 2009;**23**(3):211–217.
-
- 64.** Diehl-Schmid J, Forstl H, Perneczky R, Pohl C, Kurz A. A 6-month, open-label study of memantine in patients with frontotemporal dementia. *Int J Geriatr Psychiatry* 2008;**23**(7):754–759.
-
- 65.** Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, Mendez M, Kerwin D, Lerner A, Wu CK *et al.* Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2013;**12**(2):149–156.
-
- 66.** Finger EC. New potential therapeutic approaches in frontotemporal dementia: oxytocin, vasopressin, and social cognition. *J Mol Neurosci* 2011;**45**(3):696–701.
-
- 67.** Jesso S, Morlog D, Ross S, Pell MD, Pasternak SH, Mitchell DG, Kertesz A, Finger EC. The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. *Brain* 2011;**134**(Pt 9):2493–2501.
-
- 68.** Korte KB, Rogalski EJ. Behavioural interventions for enhancing life participation in behavioural variant frontotemporal dementia and primary progressive aphasia. *Int Rev Psychiatry* 2013;**25**(2):237–245.

Chapter 4

Behavioral variant frontotemporal dementia



Katya Rascovsky

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

The behavioral variant of frontotemporal dementia (bvFTD) is a clinical syndrome characterized by progressive deterioration of social behavior and cognitive functions. It is the most common clinical presentation of frontotemporal lobar degeneration (FTD), accounting for 56% of cases within the cognitive FTD spectrum [1]. The syndrome is male predominant and tends to present in the mid to late fifties, with a median age of onset of 58 years [2]. Compared with other dementias, bvFTD has a relatively rapid rate of progression, with death occurring an average of three to four years from initial diagnosis, and approximately eight years from symptom onset [3].

Clinically, the syndrome is characterized by disinhibition, apathy, loss of empathy, compulsive behaviors, dietary changes, and executive dysfunction [2]. Patients with bvFTD may also exhibit altered decision-making, inappropriate social and moral judgments, and difficulty decoding the emotions and mental states of others [4]. This pattern of impairment is associated with a progressive degeneration of the frontal and anterior temporal lobes (see [Figure 4.1](#)). Atrophy initially presents in orbitofrontal, anterior cingulate, anterior insular, and anterior temporal cortices, but extends to more lateral and posterior frontotemporal regions as the disease progresses [5].

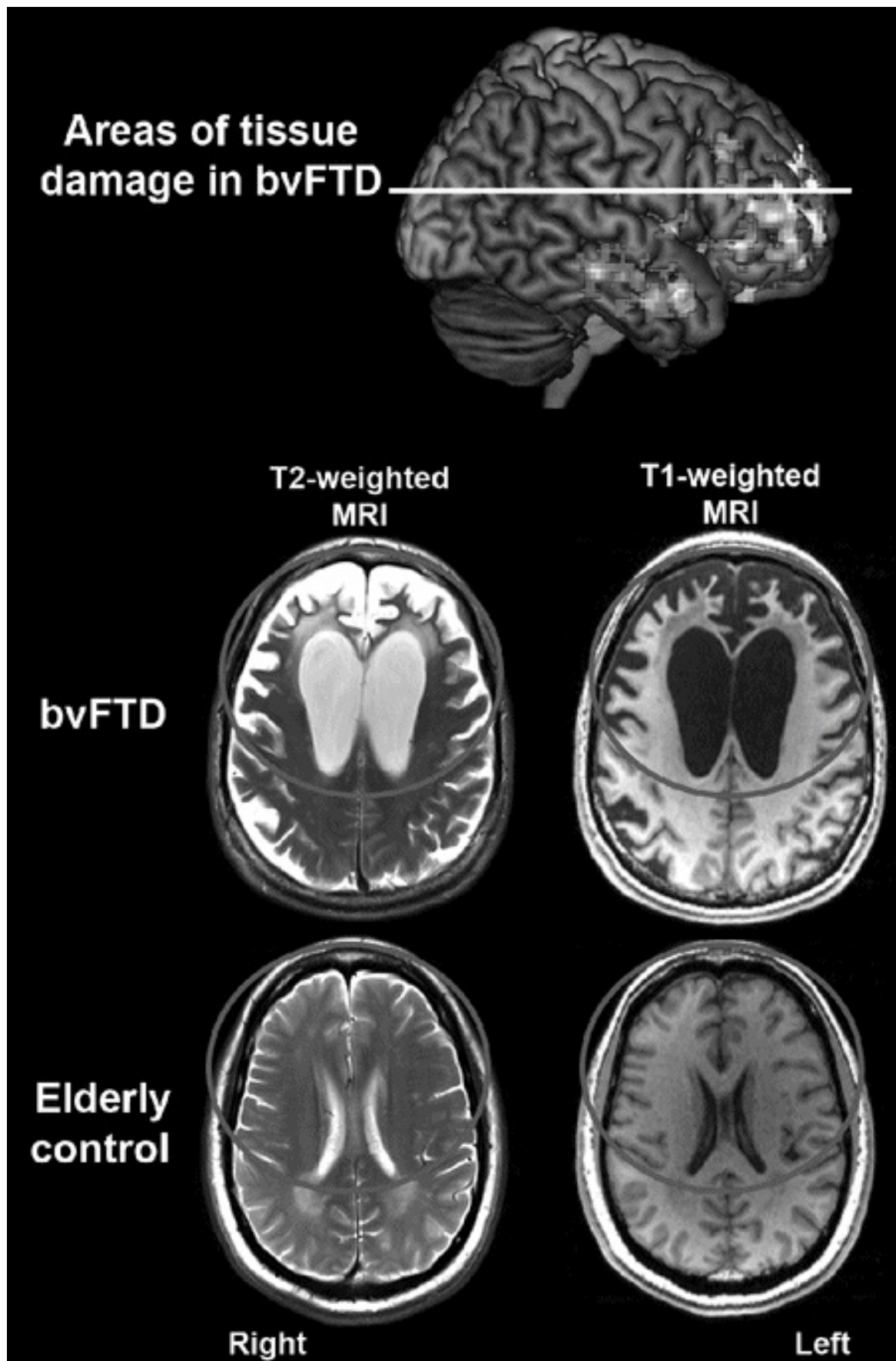


Figure 4.1 Upper panel: Regions of significantly reduced gray matter density

in a group of 19 bvFTD patients relative to 25 age- and education-matched controls. Lower panel: Comparative axial slices of a 63-year-old bvFTD patient and a 60-year-old healthy control subject.

This chapter will review the characteristic cognitive and behavioral changes associated with bvFTD, as well as recent advances and controversies in the field. The preceding chapters provide historical and general overviews of bvFTD in the context of other phenotypes of FTLD. The assessment and differential diagnosis of FTD is briefly reviewed in [Chapter 3](#) and detailed further in [Chapter 8](#), while neuropsychological and neuroimaging features of bvFTD will be described in more detail in [Chapters 9](#) and [10](#), respectively.

Diagnosis of bvFTD

The insidious behavioral changes of bvFTD can be difficult to recognize as a syndrome, and are often mistaken for psychiatric disorders of midlife. In fact, almost 50% of bvFTD patients are diagnosed with a primary psychiatric illness before their syndrome is identified as a neurodegenerative condition [\[6\]](#). Despite these challenges, early and accurate diagnosis of bvFTD is important, as it allows for appropriate therapeutic and behavioral patient management, as well as tailored family counseling and support.

Based on accumulated experience and previous diagnostic criteria [\[7–9\]](#), the International bvFTD Criteria Consortium (FTDC) developed revised guidelines for the diagnosis of bvFTD [\[2\]](#) (see [Table 4.1](#)). Diagnosis of possible bvFTD is based solely on the clinical syndrome and aims to identify patients at the mildest stages of disease. It allows for variable presentation at onset by relying on the flexible combination of

three of six clinical features: disinhibition, apathy/inertia, loss of empathy, perseverative/compulsive behaviors, hyperorality, and a dysexecutive neuropsychological profile. A diagnosis of probable bvFTD attempts to classify patients with a high probability of underlying frontotemporal degeneration, and is based on the clinical syndrome plus documented functional decline and frontotemporal imaging changes. The FTDC criteria have good inter-rater reliability [10], and large pathology-confirmed studies suggest they have encouragingly high sensitivity and specificity [2, 11]. In a sample of 146 non-aphasic young-onset dementia patients with pathology information (64 FTD, 82 non-FTD), the classification of possible bvFTD showed a sensitivity of 95% and a specificity of 82%, while probable bvFTD had a sensitivity of 85% and a specificity of 95% [11]. When possible, use of diagnostic criteria should be coupled with valid diagnostic methods that are practical and easily available in general clinical settings.

Table 4.1 International Consensus Criteria for bvFTD (FTDC)

I. Neurodegenerative disease

A. Patient must show progressive deterioration of behavior and/or cognition by observation or history

II. Possible bvFTD

Three of six behavioral/cognitive symptoms must be present to meet criteria.

A. Early behavioral disinhibition

B. Early apathy or inertia

C. Early loss of sympathy or empathy

D. Early perseverative, stereotyped, or compulsive/ritualistic behavior

E. Hyperorality and dietary changes

F. Neuropsychological profile of executive/generation deficits with relative sparing of memory and visuospatial functions

III. Probable bvFTD

All three features must be present to meet criteria.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or functional scales)

C. Imaging results consistent with bvFTD (i.e., frontal and/or anterior temporal atrophy on CT or MRI, or frontal hypoperfusion or hypometabolism on SPECT or PET)

IV. bvFTD with definite frontotemporal degeneration pathology

Criterion A and either Criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD

B. Histopathologic evidence of frontotemporal degeneration

C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

A. Deficits are better accounted for by other non-degenerative nervous system or medical disorders

B. Behavioral disturbance is better accounted for by a psychiatric diagnosis

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative disorder

Adapted from Rascovsky K, Hodges JR, Knopman D, *et al.* (2011).
Sensitivity of revised diagnostic criteria for the behavioural variant of

frontotemporal dementia. *Brain*, 134, 2456–77.

Below we describe the constellation of behavioral and cognitive features that define the bvFTD clinical syndrome, as well as methods for ascertainment and measurement of these changes.

Behavior in bvFTD

Behavioral disinhibition

Behavioral disinhibition is the hallmark feature of bvFTD and can manifest as loss of manners and decorum; socially inappropriate behavior; or impulsive, rash, or careless actions. bvFTD patients often engage in behaviors that violate social graces, such as inappropriate laughter; cursing and loudness; or crude, childish, or sexually explicit remarks. They may also exhibit a general lack of etiquette (e.g., failing to wait in line), loss of respect for interpersonal space, and poor response to social cues (e.g., patient continues to talk despite other's attempts to end a conversation). As the disease progresses, patients may present more extreme violations of social norms, such as approaching, touching, or kissing strangers; verbal or physical aggression; and inappropriate sexual acts. Disinhibition can also manifest as impulsive behaviors, which may or may not be performed in a social context. These include reckless driving, stealing (usually food or “shiny” objects), new-onset gambling, buying or selling objects without regard for consequences, or indiscriminate sharing of personal information (e.g., credit card numbers). In extreme cases, inappropriate behaviors may amount to minor criminal offenses or devastating financial decisions [[12](#), [13](#)].

Many comparative studies show that disinhibition discriminates bvFTD from other dementias in clinical and pathology-confirmed samples

[11, 14–20] (for review see [21]). Structural imaging studies have associated behavioral disinhibition with damage to orbitofrontal [22, 23] and right anterior temporal regions [24]. Consistent with these structural findings, PET and SPECT studies have associated disinhibition with the presence of orbitofrontal, ventromedial, and temporal metabolic dysfunction, particularly in the right hemisphere [25, 26].

Apathy and inertia

Apathy is defined as a loss of motivation, drive, or interest, which can manifest as passivity, lack of spontaneity, or inertia. bvFTD patients cease to engage in important or previously rewarding pursuits such as jobs, hobbies, or household responsibilities, and often seem content with sedentary activities (e.g., watching television all day). In extreme cases, patients may present with frank inertia, requiring prompts to initiate or continue basic activities of daily living. This lack of initiative is also reflected in communication, as bvFTD patients often have trouble initiating or sustaining conversations.

Apathy is the most common initial symptom of bvFTD, and appears to be more severe and pervasive in bvFTD than in other dementias [16, 17, 21, 27, 28]. In early stages, apathy is often mistaken for depression, but apathy in bvFTD is rarely associated with dysphoric mood [27]. Passivity and inertia can be extremely distressing for caregivers, as they unsuccessfully attempt to find activities that will engage the patient's interest [28]. Voxel-based morphometry studies show that severity of apathy (as measured by the Neuropsychiatric Inventory) correlates to atrophy in anterior cingulate, dorsolateral, and orbitofrontal cortices [21, 22]. This is largely consistent with SPECT imaging studies, which associate apathy with medial frontal and cingulate hypoperfusion [25], or bilateral frontal hypoperfusion [26].

Loss of empathy

Loss of empathy refers to an inability to read the emotional expressions of others or imagine their experiences [29]. It can be particularly distressing for caregivers, as the patient appears indifferent to the feelings of loved ones and family members. In day-to-day life, bvFTD patients may engage in hurtful or insensitive comments (e.g., mocking someone's physical appearance), or show outward disregard for others' physical pain or emotional distress (e.g., laughing at someone's loss or disability). Some patients exhibit a more general decline in social engagement, with emotional detachment, coldness, and lack of eye contact [25]. Caregivers and friends may experience the patient as uncharacteristically distant, as he/she no longer touches, hugs, or seeks their company.

Loss of empathy is a common feature at initial presentation and may be particularly useful in the differentiation of bvFTD from other dementias [11, 17, 20]. In fact, one study suggests that loss of empathy may be the most specific feature of bvFTD, with 90% specificity for distinguishing bvFTD with FTD pathology from other pathology-confirmed dementias [11]. This specificity may mirror the neuroanatomical substrates of empathy in general. For example, Rankin and colleagues [29] found that empathy scores in the Interpersonal Reactivity Index were significantly correlated with right frontotemporal regions. Similarly, Eslinger and colleagues found that cognitive aspects of empathy (such as perspective-taking) correlated with integrity of prefrontal and anterior temporal cortex, while empathic emotions (such as empathic concern) correlated with integrity of right medial frontal regions [30].

Perseverative, stereotyped, and compulsive behaviors

bvFTD patients often engage in simple and complex compulsive behaviors [21]. Simple repetitive behaviors include tapping, scratching, rubbing, picking at skin or clothing, rocking, humming, pursing of lips, or lip smacking. bvFTD patients can also engage in complex, compulsive, or ritualistic behaviors, with or without an obsessive component. Examples include collecting or hoarding, counting, checking, ordering or cleaning rituals, repetitive trips to the bathroom (without need), walking fixed routes, or engaging in rituals with fixed time intervals (e.g., going to the store at specific times). Perseveration can also be evident in language production, as bvFTD patients habitually repeat words, phrases, or entire stories despite their lack of communicative value.

Perseverative, stereotyped, or compulsive behaviors consistently discriminate bvFTD from other primary dementias [14–17, 31, 32], and are commonly observed in pathology-confirmed cases [2, 11]. Despite their prevalence, only a few imaging studies have explored the neuroanatomical substrates of compulsive behavior in bvFTD. While simple, stereotyped behaviors are associated with right frontal hypoperfusion on SPECT [26], complex repetitive behaviors seem to emerge in conjunction with temporal lobe atrophy [33].

Hyperorality and dietary changes

Hyperorality and dietary changes are common manifestations of bvFTD, and can range from binge eating and altered food preferences to ingestion of inedible objects. Patients often experience significant weight gain given their new cravings for sweets and other carbohydrates. Some bvFTD patients can engage in binge eating and continue to eat despite acknowledging satiety [34]. They may also exhibit rigid, stereotyped, or idiosyncratic food preferences, such as restricting intake to a particular food

(e.g., bananas), or demanding unusual food combinations. In extreme cases, hyperorality may manifest as oral exploration or ingestion of inedible objects, a feature consistent with the Klüver–Bucy syndrome [21].

Although this feature can be shared with other FTD syndromes (e.g., semantic variant primary progressive aphasia), dietary changes consistently discriminate bvFTD from dementias with other pathologic substrates [11, 19]. Recent findings suggest that increased food consumption in bvFTD is associated with orbitofrontal atrophy, while increased preference for sweets is associated with atrophy in the orbitofrontal cortex and right insula [34, 35]. A clinicopathologic study of eating behavior in bvFTD found that hyperorality was associated with neuronal dropout in the hypothalamus, a crucial structure for eating and metabolic needs [36].

Measuring behavior in bvFTD

While many researchers agree on the core behavioral features that constitute the bvFTD syndrome, there is no consensus regarding the optimal tools and methods required to measure these behavioral alterations. Identifying and measuring behavioral change in bvFTD is difficult for several reasons. First, rating of features such as “disinhibition” can be subjective and depend on culture and situational context [37]. For example, cursing or sexually explicit jokes may be acceptable amongst close friends, but considered inappropriate at work, school, or religious settings. Second, behavioral changes in midlife are rarely recognized as a reflection of neurodegenerative disease, often leading to provisional psychiatric diagnoses such as bipolar disorder, depression, or even late-life schizophrenia [6]. A bvFTD diagnosis is further confounded if the patient has a long-standing history of “odd” or “eccentric” behavior, or when the

primary informant has limited contact with the patient (e.g., siblings or children living in separate households).

With these caveats in mind, how can we ascertain and measure the behavioral changes typical of bvFTD? We can generally divide these approaches into subjective and objective methods. Subjective self-report scales are commonly used to measure internal states, self-reported behavioral patterns, beliefs, or personal preferences. Given the lack of introspection typical of bvFTD, these scales can be misleading and should not be relied upon for diagnosis. Caregiver surveys circumvent issues of insight and have the added advantage of providing information about the patient in context (e.g., at home) and over long periods of time. For quantification of these behaviors, many researchers rely on informant-based scales such as the Neuropsychiatric Inventory (NPI) [38], Frontal Behavioral Inventory (FBI) [17], or the Cambridge Behavioural Inventory [15, 39]. Although caregiver questionnaires represent an improvement over self-report measures, these ratings are still inherently subjective. It may be difficult for caregivers to make inferences about the patient's thoughts, mood, or motivation. Furthermore, the severity of reported symptoms may be colored by the overall health, stress, and personality of the caregiver [40]. Given these concerns, rating of aberrant comportment should be based on overt behaviors as opposed to inferences about a patient's cognitive or emotional state.

Objective methods for rating behavior include clinical observation and objective testing. Unfortunately, there are few clinician-based scales for rating and measuring abnormal behavior in neurodegenerative disease. Notably, Rankin and colleagues [18] developed the Social Observer Behavior Checklist, which quantifies spontaneous social behavior during routine cognitive evaluations. This checklist allows clinicians to rate observable behavioral changes, such as perseveration or disregard for

social norms. Although clinician-based scales can provide objective behavioral ratings, this information is inevitably limited by time and context. Patients will rarely exhibit florid disinhibited or perseverative behaviors in a one-hour clinical or cognitive evaluation. Furthermore, these scales cannot evaluate behaviors that occur at home such as changes in sleep, food intake, or daily routines. The clinical context may also mitigate spontaneous aberrant behaviors by introducing a significant amount of external structure, in a way acting as the patient's “frontal lobes” [37]. Given the shortcomings of subjective measures and clinical observation, researchers are moving towards objective, patient-based tests capable of quantifying characteristic bvFTD behaviors. Novel patient-based approaches are already available to test apathy/inertia [28, 41], disinhibition [23], and environmental dependency [42]. As with most clinical assessments, a combination of objective and subjective methods may provide the best approach for rating and quantifying abnormal behavior. For example, Bickart, Dickerson, and colleagues [43] developed a hybrid scale that measures social change in FTD by combining observable behavioral signs with a structured caregiver interview. In the future, these novel approaches may complement objective patient-based methods to reliably quantify and track abnormal behavior in bvFTD. See [Chapters 3](#) and [8](#) for additional discussion about differential diagnosis in patients with a history of symptoms consistent with bvFTD.

Cognition in bvFTD

While behavioral changes tend to dominate the initial presentation of bvFTD, cognitive deficits inevitably appear with disease progression. When these impairments emerge, the resulting cognitive profile is usually

characterized by executive and generation deficits in the context of relatively preserved memory and visuospatial functions [2, 11, 44]. The distinct components of the bvFTD cognitive profile are described below.

Executive and generation deficits

When discussing impairments in so-called “executive functions,” one should keep in mind that this overarching term includes a wide variety of abilities, including generation, planning, inhibition, problem-solving, set-shifting, and abstraction. Given this inclusive definition, it is not surprising that the utility of traditional executive tasks for differential diagnosis of bvFTD remains a matter of debate.

Probably the most consistent neuropsychological finding in this population is a disproportionate deficit in “phonemic” or “letter” fluency, a verbal fluency task that requires retrieval and organizational strategies dependent on the frontal lobes [45, 46]. While several studies report greater fluency, abstraction, and cognitive flexibility deficits in bvFTD compared with Alzheimer's disease (AD) [23, 44, 45, 47, 48], others fail to distinguish dementia groups based on traditional executive tasks such as the Wisconsin Card Sorting Test (WCST) or the Stroop Test [44, 49]. As with any cognitive construct, a combination of executive measures may prove more useful for differential diagnosis than comparisons based on individual test performance. For example, one study found adequate discrimination of bvFTD and AD patients using the INECO Frontal Screening (IFS) [50], while another study showed 89% correct classification of bvFTD and AD patients based on their performance on letter fluency, digit span backward, and the Hayling Test of response inhibition [51]. Interestingly, some reports suggest that presence of dysexecutive errors during a cognitive evaluation may be particularly useful in the diagnosis of bvFTD. For example, one

study found that a composite measure of perseverations and rule-violations discriminated between bvFTD and AD [52], while another study found that qualitative features such as concrete thought, perseveration, confabulation, and poor organization enhanced differential diagnosis of bvFTD over and above discrimination based on cognitive achievement scores [53].

From the above brief review, it should be clear that the value of traditional “executive” measures in the differential diagnosis of bvFTD is still open to question [49]. There are several theoretical explanations for these seemingly inconsistent results. First, executive deficits, while present in bvFTD, are not specific to this condition. Executive impairments can occur in AD and are common in syndromes with prominent fronto-subcortical dysfunction such as progressive supranuclear palsy and Parkinson's disease. Second, most traditional executive tasks measure dorsolateral integrity rather than orbitofrontal/ventromedial functioning, the latter believed to be more severely compromised in early stages of bvFTD [5]. Finally, the sensitivity of executive tasks in early diagnosis may be attenuated by the inherent structure of cognitive assessments. For this reason, some researchers advocate the use of ecologically valid planning and organizing tasks (e.g., Multiple Errands Test), which may better reflect the everyday dysexecutive errors of bvFTD patients [54].

Relative preservation of visuospatial and constructional abilities

Most bvFTD patients retain the capacity to copy simple line drawings, assemble blocks, and judge spatial positions until very late in their disease. This finding is consistent with caregiver reports of relatively preserved topographic orientation and day-to-day spatial and constructional abilities [20]. The relative sparing of visuospatial and constructional functions is particularly useful when attempting to differentiate bvFTD from other

dementias [47, 55], and may reflect the typical sparing of occipital and parietal regions early in the disease course (see [Figure 4.1](#)). When evaluating patients with bvFTD, care should be taken to avoid complex spatial or constructional tasks, as performance on these tasks may be confounded by attentional or organizational requirements dependent on the frontal lobes.

Relative preservation of episodic memory

Preservation of episodic memory (relative to executive dysfunction) can be very valuable in differential diagnosis, particularly when the distinction involves bvFTD and AD [44, 49]. The distinction is especially clear when using memory tests that lack heavy retrieval or executive demands (e.g., short word lists or recall of simple figures). The relative sparing of episodic memory in bvFTD versus AD has been demonstrated in both verbal and visuospatial modalities [44, 47, 52]. Furthermore, longitudinal studies demonstrate a more rapid decline of episodic memory in AD compared with bvFTD [56]. This disparate memory performance is likely to reflect greater medial temporo-limbic pathology in AD compared to an early sparing of these structures in bvFTD [57]. However, relative sparing of episodic memory in bvFTD should not be interpreted as evidence of “intact” memory function. Recent reports indicate that episodic memory deficits in bvFTD are more common than previously thought [58]. Of note, marked anterograde amnesia has been documented as either the sole or dominant symptom in up to 10% of pathology-confirmed bvFTD cases [59]. Amnestic presentations appear to be more frequent in elderly bvFTD subjects [2], and may be related to the presence of concomitant hippocampal sclerosis [60].

Measuring cognition in bvFTD

When using neuropsychology to differentiate bvFTD from other disorders, it is important to keep several things in mind. First, just as there is no single behavioral symptom that can differentiate bvFTD from other dementias, there may be no single neuropsychological test that can differentiate between dementia groups [49]. Rather, clinicians must look at the overall cognitive profile, i.e., executive deficits in the context of relatively preserved memory and visuospatial functions. In a large, pathology-confirmed dementia cohort [11], the presence of this cognitive profile had a sensitivity of 91% and a specificity of 83% for identifying bvFTD with FTD pathology. Of note, quantitative studies show that this neuropsychological profile discriminates between autopsy-confirmed bvFTD and AD patients [47] and appears relatively stable throughout the disease course [48]. Second, when using cognitive performance in differential diagnosis, clinicians should be mindful of both pattern and chronology of deficits. For example, patients presenting with severe spatial disorientation as their initial symptom are unlikely to have the focal frontotemporal atrophy characteristic of early bvFTD. Finally, the ability to detect differences between dementia groups may be enhanced or attenuated by the particular choice of neuropsychological tests. Because frontal lobe dysfunction can confound the results of testing in other cognitive domains, care must be taken to choose neuropsychological tests that minimize executive demands (e.g., working memory, planning, or set-shifting). See [Chapter 9](#) for additional discussion of cognitive assessment of patients with suspected bvFTD.

Emotion, social cognition, and decision-

making in bvFTD

In everyday life, bvFTD patients exhibit poor judgment, impulsive behaviors, and difficulty decoding the emotions and mental states of others. These alterations are particularly difficult for caregivers, and can lead to animosity, distress, and marital dissatisfaction [61]. Given that traditional neuropsychological tests are not designed to capture these impairments, new tools have been proposed to assess emotion, social cognition, and decision-making in bvFTD.

Emotion and social cognition

bvFTD patients appear to have significant impairments in the recognition of negative emotions such as sadness, anger, fear, and disgust [62, 63]. These recognition deficits have been associated with damage to a right-predominant network involving orbitofrontal cortex, amygdala, insula, and lateral and inferior aspects of the temporal lobe [62, 63]. Interestingly, bvFTD patients also show prominent alterations in the experience and expression of self-conscious emotions such as amusement or embarrassment [64]. Difficulties processing negative and self-conscious emotions may contribute to the loss of empathy and insensitivity to social disapproval typical of patients with bvFTD.

Social deficits in bvFTD patients may also be explained by their reported impairments in mentalizing or theory of mind (ToM). ToM is defined as the ability to assess the beliefs, desires, and intentions of other people and is thought to be critically subserved by rostral aspects of the medial prefrontal cortex [65]. Several tasks have been used to examine ToM in bvFTD. In first- and second-order false belief tasks, subjects are asked to assess a character's belief about a situation (e.g., X believes Y), or a character's belief about another character's thoughts or intentions (e.g., X

believes that Z believes Y). Some ToM tasks require additional emotional attributions, such as the Reading of the Mind in the Eyes Test (where subjects identify the feelings of an individual from a photograph of their eyes) or the Faux Pas Test (where subjects determine whether a character committed an embarrassing social faux pas). While bvFTD patients exhibit variable deficits in first- and second-order false belief tasks, they often fail tests of emotional attribution [54]. Of note, most ToM tests use stories, vignettes, or cartoons that require adequate integration of multiple cognitive abilities. Several studies have found a relationship between ToM performance and executive dysfunction in bvFTD, making it difficult to ascribe failure in complex ToM tasks to a selective deficit in mentalizing or perspective-taking [30, 66].

Although bvFTD patients may act in ways that are contrary to social mores [12, 13], they appear to have preserved knowledge of moral rules and conventional norms [67, 68]. However, when resolving hypothetical moral dilemmas, bvFTD patients are more likely to provide “utilitarian” responses compared with AD patients and normal controls [68]. For example, in the hypothetical “footbridge dilemma,” bvFTD patients are more likely to push an innocent man off a footbridge (thus murdering him), in order to save the life of five workers who would otherwise be killed by an approaching train [68, 69]. This abnormal utilitarian response has been replicated using other emotional moral dilemmas and appears to be linked to dysfunction in right frontotemporal regions [68].

Decision-making

bvFTD patients are known to make poor personal and financial choices in their everyday lives. However, it is difficult to replicate these poor judgments in the context of a traditional cognitive evaluation. Decision-

making in bvFTD can be formally studied using experimental tasks that vary risk, punishment, and reward [70]. For example, several studies have used the Iowa Gambling Task (IGT), where participants choose cards from decks that yield a particular pattern of rewards. As the game proceeds, normal subjects adopt a conservative strategy of accepting small wins in order to avoid large losses, while bvFTD patients consistently choose cards from decks that offer large wins and even greater losses [54]. Although bvFTD patients exhibit clear impairments in the IGT, care should be taken when interpreting these results. Performance in the IGT may be confounded by task-related failures in a variety of cognitive abilities including working memory, probability assessment, reversal learning, or stimulus-reinforcement learning, all functions subserved by the frontal lobes [71]. Another approach to the study of decision-making evaluates the use of context using real-world scenarios. In one study, bvFTD patients were asked to judge the relative acceptability of scenarios embellished with a positive, socially rewarding context (e.g., going through a red light when rushing a sick child to the hospital) or a negative, socially penalizing context (e.g., going through a red light when a police car is stationed at the intersection) [72]. Compared with AD patients and controls, bvFTD patients appropriately shifted their acceptability judgments of positively valenced scenarios but were insensitive to the socially penalizing context of negative scenarios. From the above review, it should be clear that “decision-making” is a complex construct that depends on multiple cognitive abilities and brain regions [70]. Further research is required to elucidate the pattern and neuroanatomical substrates of altered decision-making in bvFTD.

Experimental tasks in clinical practice

Compared with traditional cognitive tasks, performance on experimental tasks of emotion, social cognition, and decision-making may better reflect the everyday difficulties faced by bvFTD patients. However, further work is required before these novel approaches are implemented in standard clinical practice. First, the utility of these tasks in the differential diagnosis of bvFTD is still open to question. Although originally designed as measures of ventromedial and orbitofrontal integrity, most of these tasks are complex and demand multiple cognitive abilities dependent on other brain regions [71]. This inherent complexity can lead to lack of diagnostic specificity. For example, recent reports show that patients with a range of neurodegenerative conditions can exhibit comparable deficits in tests of decision-making [70], ToM [66], and emotional tracking and recognition [66, 73]. Second, the use of experimental tasks in routine clinical practice must balance practical and theoretical concerns. Most of these tasks are time-consuming and demand specialized stimuli and training. Wide adoption of these tasks will require the development of short and simple versions specifically designed for use in general clinical settings [74]. The diagnostic value of these novel approaches will ultimately depend on their ability to discriminate over and above the often-robust cognitive and behavioral profiles obtained by existing tests and questionnaires.

Conclusions

bvFTD is the most common clinical presentation of frontotemporal degeneration, affecting relatively young people in the prime of their productive years. Clinically, the syndrome is characterized by disinhibition, apathy, loss of empathy, compulsive behaviors, dietary changes, and executive dysfunction. Patients with bvFTD may also exhibit alterations in

emotional reactivity, social cognition, and everyday decision-making. We hope that increased recognition of the bvFTD clinical profile will lead to better diagnosis, counseling, and care for patients and their families. The study of the cognitive and behavioral characteristics of bvFTD may also prove invaluable for the emerging field of social neuroscience. Given their profound behavioral deficits and known damage to key components of the “social” brain, bvFTD patients may provide a window into the function and dysfunction of the neural structures that make us truly human.

Acknowledgment

The author would like to acknowledge the assistance of Drs. Corey McMillan and Murray Grossman at the Penn Frontotemporal Degeneration Center.

Funding: This work was supported by AG17586, AG32953, NS44266, AG15116, AG38490, AG43503, NS53488, AG046499, and the Wyncote Foundation.

References

1. Johnson JK, Diehl J, Mendez MF, Neuhaus J, Shapira JS, Forman M, *et al.* Frontotemporal lobar degeneration: demographic characteristics of 353 patients. *Arch Neurol* 2005;**62**:925–30.
2. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;**134**:2456–77.
3. Garcin B, Lillo P, Hornberger M, Piguet O, Dawson K, Nestor PJ, *et al.*

Determinants of survival in behavioral variant frontotemporal dementia. *Neurology* 2009;**73**:1656–61.

4. Rascovsky K, Grossman M. Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration. *Int Rev Psychiatry* 2013;**25**:145–58.

5. Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, *et al*. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol* 2008;**65**:249–55.

6. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry* 2011;**72**:126–33.

7. Brun A, Englund B, Gustafson L, Passant U, Mann DMA, Neary D, *et al*. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 1994;**57**:416–18.

8. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, *et al*. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;**51**:1546–54.

9. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001;**58**:1803–9.

10. Lamarre AK, Rascovsky K, Bostrom A, Toofanian P, Wilkins S, Sha SJ, *et al*. Interrater reliability of the new criteria for behavioral variant frontotemporal dementia. *Neurology* 2013;**80**:1973–7.

11. Harris JM, Gall C, Thompson JC, Richardson AMT, Neary D, du Plessis D, *et al*. Sensitivity and specificity of FTDC criteria for behavioral variant

frontotemporal dementia. *Neurology* 2013;**80**:1881–7.

12. Mendez MF, Chen AK, Shapira JS, Miller BL. Acquired sociopathy and frontotemporal dementia. *Dement Geriatr Cogn Disord* 2005;**20**:99–104.

13. Diehl-Schmid J, Perneczky R, Koch J, Nedopil N, Kurz A. Guilty by suspicion? Criminal behavior in frontotemporal lobar degeneration. *Cogn Behav Neurol* 2013;**26**:73–7.

14. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 2001;**103**:367–78.

15. Bozeat S, Gregory CA, Ralph MA, Hodges JR. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2000;**69**:178–86.

16. de Vugt ME, Riedijk SR, Aalten P, Tibben A, van Swieten JC, Verhey FRJ. Impact of behavioural problems on spousal caregivers: a comparison between Alzheimer's disease and frontotemporal dementia. *Dement Geriatr Cogn Disord* 2006;**22**:35–41.

17. Kertesz A, Nadkarni N, Davidson W, Thomas AW. The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. *J Int Neuropsychol Soc* 2000;**6**:460–8.

18. Rankin KP, Santos-Modesitt W, Kramer JH, Pavlic D, Beckman V, Miller BL. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry* 2008;**69**:60–73.

19. Rosen HJ, Hartikainen KM, Jagust W, Kramer JH, Reed BR, Cummings JL, *et al.* Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. *Neurology* 2002;**58**:1608–15.

-
- 20.** Barber R, Snowden JS, Craufurd D. Frontotemporal dementia and Alzheimer's disease: retrospective differentiation using information from informants. *J Neurol Neurosurg Psychiatry* 1995;**59**:61–70.
-
- 21.** Mendez MF, Lauterbach EC, Sampson SM. An evidence-based review of the psychopathology of frontotemporal dementia: a report of the ANPA Committee on Research. *J Neuropsychiatry Clin Neurosci* 2008;**20**:130–49.
-
- 22.** Massimo L, Powers C, Moore P, Vesely L, Avants B, Gee J, *et al.* Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord* 2009;**27**:96–104.
-
- 23.** Hornberger M, Geng J, Hodges JR. Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia. *Brain* 2011;**134**:2502–12.
-
- 24.** Zamboni G, Huey ED, Krueger F, Nichelli PF, Grafman J. Apathy and disinhibition in frontotemporal dementia: insights into their neural correlates. *Neurology* 2008;**71**:736–42.
-
- 25.** Le Ber I, Guedj E, Gabelle A, Verpillat P, Volteau M, Thomas-Anterion C, *et al.* Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. *Brain* 2006;**129**:3051–65.
-
- 26.** McMurtray AM, Chen AK, Shapira JS, Chow TW, Mishkin F, Miller BL, *et al.* Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. *Neurology* 2006;**66**:517–22.
-
- 27.** Chow TW, Binns MA, Cummings JL, Lam I, Black SE, Miller BL, *et al.* Apathy symptom profile and behavioral associations in frontotemporal dementia vs dementia of Alzheimer type. *Arch Neurol* 2009;**66**:888–93.
-
- 28.** Merrilees J, Dowling GA, Hubbard E, Mastick J, Ketelle R, Miller BL.

Characterization of apathy in persons with frontotemporal dementia and the impact on family caregivers. *Alzheimer Dis Assoc Disord* 2013;**27**:62–7.

29. Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, *et al.* Structural anatomy of empathy in neurodegenerative disease. *Brain* 2006;**129**:2945–56.

30. Eslinger PJ, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. *J Neuropsychiatry Clin Neurosci* 2011;**23**:74–82.

31. Mendez MF, Shapira JS, Miller BL. Stereotypical movements and frontotemporal dementia. *Mov Disord* 2005;**20**:742–5.

32. Nyatsanza S, Shetty T, Gregory C, Lough S, Dawson K, Hodges JR. A study of stereotypic behaviours in Alzheimer's disease and frontal and temporal variant frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2003;**74**:1398–402.

33. Rosso SM, Roks G, Stevens M, de Koning I, Tanghe HL, Kamphorst W, *et al.* Complex compulsive behaviour in the temporal variant of frontotemporal dementia. *J Neurol* 2001;**248**:965–70.

34. Woolley JD, Gorno-Tempini ML, Seeley WW, Rankin K, Lee SS, Matthews BR, *et al.* Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. *Neurology* 2007;**69**:1424–33.

35. Whitwell JL, Sampson EL, Loy CT, Warren JE, Rossor MN, Fox NC, *et al.* VBM signatures of abnormal eating behaviours in frontotemporal lobar degeneration. *Neuroimage* 2007;**35**:207–13.

36. Piguet O, Petersen A, Yin Ka Lam B, Gabery S, Murphy K, Hodges JR, *et al.* Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. *Ann Neurol* 2011;**69**:312–19.

37. Ibanez A, Manes F. Contextual social cognition and the behavioral variant of frontotemporal dementia. *Neurology* 2012;**78**:1354–62.

38. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory comprehensive assessment of psychopathology in dementia. *Neurology* 1994;**44**:2308–8.

39. Wedderburn C, Wear H, Brown J, Mason SJ, Barker RA, Hodges J, *et al.* The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. *J Neurol Neurosurg Psychiatry* 2008;**79**:500–3.

40. Mioshi E, Bristow M, Cook R, Hodges JR. Factors underlying caregiver stress in frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2009;**27**:76–81.

41. Massimo L, Morgan B, Chandrasekaran K, Boller A, Camp E, Rascovsky K, *et al.* Initiation difficulty and apathy in behavioral variant frontotemporal degeneration. *Neurology* 2012;**78**:PD7001.

42. Ghosh A, Dutt A, Bhargava P, Snowden J. Environmental dependency behaviours in frontotemporal dementia: have we been underrating them? *J Neurol* 2012;**260**:861–8.

43. Bickart KC, Brickhouse M, Negreira A, Sapolsky D, Barrett LF, Dickerson BC. Atrophy in distinct corticolimbic networks in frontotemporal dementia relates to social impairments measured using the Social Impairment Rating Scale. *J Neurol Neurosurg Psychiatry* 2014;**85**:438–48. doi:10.1136/jnnp-2012-304656.

44. Wittenberg D, Possin KL, Rascovsky K, Rankin KP, Miller BL, Kramer JH. The early neuropsychological and behavioral characteristics of frontotemporal dementia. *Neuropsychol Rev* 2008;**18**:91–102.

45. Rascovsky K, Salmon DP, Hansen LA, Thal LJ, Galasko D. Disparate letter

and semantic category fluency deficits in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *Neuropsychology* 2007;**21**:20–30.

46. Libon DJ, McMillan C, Gunawardena D, Powers C, Massimo L, Khan A, *et al.* Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. *Neurology* 2009;**73**:535–42.

47. Rascovsky K, Salmon DP, Ho GJ, Galasko D, Peavy GM, Hansen LA, *et al.* Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology* 2002;**58**:1801–8.

48. Rascovsky K, Salmon DP, Hansen LA, Galasko D. Distinct cognitive profiles and rates of decline on the Mattis Dementia Rating Scale in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *J Int Neuropsychol Soc* 2008;**14**:373–83.

49. Hutchinson AD, Mathias JL. Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. *J Neurol Neurosurg Psychiatry* 2007;**78**:917–28.

50. Torralva T, Roca M, Gleichgerricht E, Lopez P, Manes F. INECO Frontal Screening (IFS): a brief, sensitive, and specific tool to assess executive functions in dementia. *J Int Neuropsychol Soc* 2009;**15**:777–86.

51. Hornberger M, Savage S, Hsieh S, Mioshi E, Piguet O, Hodges JR. Orbitofrontal dysfunction discriminates behavioral variant frontotemporal dementia from Alzheimer's disease. *Dement Geriatr Cogn Disord* 2010;**30**:547–52.

52. Kramer JH, Jurik J, Sha SJ, Rankin KP, Rosen HJ, Johnson JK, *et al.* Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cogn Behav Neurol* 2003;**16**:211–18.

53. Thompson JC, Stopford CL, Snowden JS, Neary D. Qualitative neuropsychological performance characteristics in frontotemporal dementia and

Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2005;**76**:920–7.

54. Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain* 2009;**132**:1299–309.

55. Mendez MF, McMurtray AM, Licht EA, Saul RE. Frontal-executive versus posterior-perceptual mental status deficits in early-onset dementias. *Am J Alzheimers Dis Other Demen* 2009;**24**:220–7.

56. Xie SX, Libon DJ, Wang X, Massimo L, Moore P, Vesely L, *et al.* Longitudinal patterns of semantic and episodic memory in frontotemporal lobar degeneration and Alzheimer's disease. *J Int Neuropsychol Soc* 2010;**16**:278–86.

57. Avants BB, Libon DJ, Rascovsky K, Boller A, McMillan CT, Massimo L, *et al.* Sparse canonical correlation analysis relates network-level atrophy to multivariate cognitive measures in a neurodegenerative population. *Neuroimage* 2014;**84**:698–711.

58. Hornberger M, Piguet O, Graham AJ, Nestor PJ, Hodges JR. How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology* 2010;**74**:472–9.

59. Graham A, Davies R, Xuereb J, Halliday G, Kril J, Creasey H, *et al.* Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* 2005;**128**:597–605.

60. Baborie A, Griffiths TD, Jaros E, McKeith IG, Burn DJ, Richardson A, *et al.* Pathological correlates of frontotemporal lobar degeneration in the elderly. *Acta Neuropathol* 2010;**121**:365–71.

61. Ascher EA, Sturm VE, Seider BH, Holley SR, Miller BL, Levenson RW. Relationship satisfaction and emotional language in frontotemporal dementia and Alzheimer disease patients and spousal caregivers. *Alzheimer Dis Assoc Disord* 2010;**24**:49–55.

-
- 62.** Kipps CM, Nestor PJ, Acosta-Cabronero J, Arnold R, Hodges JR. Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing. *Brain* 2009;**132**:592–603.
-
- 63.** Werner KH, Roberts NA, Rosen HJ, Dean DL, Kramer JH, Weiner MW, *et al.* Emotional reactivity and emotion recognition in frontotemporal lobar degeneration. *Neurology* 2007;**69**:148–55.
-
- 64.** Sturm VE, Ascher EA, Miller BL, Levenson RW. Diminished self-conscious emotional responding in frontotemporal lobar degeneration patients. *Emotion* 2008;**8**:861–9.
-
- 65.** Adenzato M, Cavallo M, Enrici I. Theory of mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels. *Neuropsychologia* 2010;**48**:2–12.
-
- 66.** Freedman M, Binns MA, Black SE, Murphy C, Stuss DT. Theory of mind and recognition of facial emotion in dementia: challenge to current concepts. *Alzheimer Dis Assoc Disord* 2013;**27**: 56–61.
-
- 67.** Mendez MF, Anderson E, Shapira JS. An investigation of moral judgement in frontotemporal dementia. *Cogn Behav Neurol* 2005;**18**:193–7.
-
- 68.** Mendez MF, Shapira JS. Altered emotional morality in frontotemporal dementia. *Cogn Neuropsychiatry* 2009;**14**:165–79.
-
- 69.** Gleichgerrcht E, Torralva T, Roca M, Pose M, Manes F. The role of social cognition in moral judgment in frontotemporal dementia. *Soc Neurosci* 2011;**6**:113–22.
-
- 70.** Gleichgerrcht E, Ibanez A, Roca M, Torralva T, Manes F. Decision-making cognition in neurodegenerative diseases. *Nat Rev Neurol* 2010;**6**:611–23.
-

71. Fellows LK, Farah MJ. Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cereb Cortex* 2005;**15**:58–63.

72. Grossman M, Eslinger PJ, Troiani V, Anderson C, Avants B, Gee JC, *et al.* The role of ventral medial prefrontal cortex in social decisions: converging evidence from fMRI and frontotemporal lobar degeneration. *Neuropsychologia* 2010;**48**:3505–12.

73. Goodkind MS, Sollberger M, Gyurak A, Rosen HJ, Rankin KP, Miller B, *et al.* Tracking emotional valence: the role of the orbitofrontal cortex. *Hum Brain Mapp* 2011;**33**:753–62.

74. Sarazin M, Dubois B, de Souza LC, Bertoux M. Should the Social Cognition and Emotional Assessment replace standard neuropsychological tests for frontotemporal dementia? *Expert Rev Neurother* 2012;**12**:633–5.

Chapter 5

Primary progressive aphasia



Chiara Cerami and Stefano F. Cappa

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

Neurodegenerative processes typically show predilection for specific neuronal types and neural systems. The language network can be selectively affected by neurodegeneration, leading to a progressive language dysfunction (primary progressive aphasia, PPA). The possible reasons for this selective susceptibility remain unknown. The reported association between a history of developmental language disorders or atypical handedness and PPA raises important issues for the neurobiology of language [1, 2]. While several reports of progressive language disorders can be found in the classical neurologic literature [3], it was only with the seminal description of slowly progressive aphasia by Mesulam [4] that PPA became a well-defined clinical entity. Following this report, an extensive amount of research has been dedicated to what soon was recognized as a

heterogeneous group of conditions, in which language impairment is the main symptom at onset, and remains the prominent clinical feature during many years of progression.

Three diagnostic criteria for PPA have been clearly defined [5]:

- (1) The patient must show an insidious onset and a gradual progression of aphasia, defined as a disorder of word and/or sentence usage (production and comprehension).
- (2) The language disorder is the only determinant on functional impairment in the activities of daily living.
- (3) On the basis of diagnostic procedures, the disorder can be univocally attributed to a neurodegenerative process.

These criteria are crucial, as a disorder of speech and language can be observed as the presentation of non-degenerative pathology (e.g., cerebrovascular pathology), or can be associated with additional cognitive disorders, leading to a functional impairment compatible with a dementia diagnosis (e.g., atypical Alzheimer's disease [AD], prion diseases, etc.). In order to increase specificity, it was originally suggested that a diagnosis of PPA required a minimum follow-up of two years [6]. While increasing specificity, this diagnostic requirement stands in contrast with the present emphasis on diagnosis at the early stages of neurodegeneration, and prevents the description of the early and mild stages of disease [7].

PPA is now considered, together with the behavioral variant (bvFTD), one of the two major clinical presentations of frontotemporal lobar degeneration (FTLD) [8]. Not all cases of PPA, however, are associated with the FTLD spectrum. Multiple neurodegenerative disorders can present with a PPA phenotype, when they are associated with a selective, or relatively selective, involvement of the language networks. As mentioned

above, the clinical pattern of PPA is extremely heterogeneous, and a careful definition of the language phenotype represents, together with the imaging findings, a powerful probabilistic predictor of the underlying pathology (see, for example, [9]). Recently, a set of criteria have been proposed for the classification of the most common PPA presentations [10]. The three main varieties (non-fluent/agrammatic [nfvPPA], semantic [svPPA], and logopenic/phono-logic [lvPPA] variant) are described on the basis of specific cognitive and linguistic features, associated with different topographic patterns of brain involvement [11].

In this chapter, we provide a review of the current knowledge of clinical and neuropsychological aspects of the main PPA syndromes. We also discuss neuroimaging features of the different phenotypical presentations, as well as of their genetic substrates in the context of the FTLD spectrum of disorders. Finally, we supply a quick look at approaches to patient treatment and management.

The role of neuropsychological assessment

The clinical evaluation of a suspected PPA patient is based on a sequence of stages. The first step is the assessment of overall cognitive status on the basis of the clinical interview, supplemented by neuropsychological testing and functional assessment. Typical subjective complaints are problems with word-finding, in particular for low-frequency words, and/or motor speech impairment, detected by the subject or by communication partners. By definition, prominent disorders of memory or visuospatial abilities should not be volunteered by the patient and/or relatives in these early stages. Neuropsychological assessment is required to provide evidence for the

selectivity of speech/language impairment. It must be underlined that many neuropsychological tests are language-based, resulting in a defective performance, for example, in verbal memory tests by PPA patients. A careful interpretation of both test profile and performance in the activities of daily living is the basis of an adequate judgment about the selectivity of the language deficit.

The second step is a detailed assessment of language abilities. A “minimal” procedure can be delineated, allowing a classification according to the current diagnostic criteria [12]:

- (1) The first, and foremost, component of the procedure is the qualitative and quantitative observation of the patient's speech and language during a semi-structured interview consisting of a complex picture description (e.g., picnic picture of the Western Aphasia Battery – [13]), as suggested by Wilson and co-workers [14]. The main parameters to be assessed are: lexical production rate and phonologic/articulatory errors; disorders of fluency (pauses and repetitions); lexical typology; and syntactic structure and complexity. On this basis, it is possible to assess the patient for the presence or absence of motor speech disorders and agrammatism, which are crucial for the differential diagnosis between nfvPPA and lvPPA (see below). The evaluation grid has been developed for English speakers, but can be adapted to other languages. An additional procedure allowing a simplified assessment of sentence production abilities is the Northwestern Anagram Test [15]. Also in this case, adaptations for different languages are under construction.
- (2) A comprehensive testing of lexical–semantic abilities is another crucial component for differential diagnosis. Ideally, it should comprise tasks of picture naming, naming from verbal description,

word–picture matching to assess single-word comprehension, and a non-verbal (picture matching) task. Further measures of semantic knowledge, based on the assessment of the ability to generate and verify semantic features about test items (“does a dog bark or meow?”) are useful for an in-depth assessment. The test items should be selected to cover different semantic categories (e.g., animals and tools), matched for lexical frequency, familiarity, and other linguistic variables [[16](#), [17](#)].

(3) A repetition test allowing an assessment of phonologic and auditory verbal short-term memory abilities is required for the diagnosis of lvPPA. It is important to include sentences with low probability meaning (such as the classical “no ifs, ands, or buts”) and of different length.

(4) Sentence–picture matching tasks enable the assessment of syntactic comprehension. These tasks can be challenging for PPA patients, in particular, if they require multiple possible responses, making considerable demands on working memory and executive processes. In this case, the selective use of high-frequency lexical items can make the task suitable for the specific investigation of syntactic abilities [[18](#)].

(5) An assessment of reading aloud can provide useful information for the diagnosis of svPPA. The presence of surface dyslexia can be disclosed by a list containing irregular words of high and low frequency [[19](#)]. Also in this case an adaptation is required for languages with different orthographic systems. In the case of transparent orthographies, such as in Italian, reading of words with irregular stress patterns can provide evidence of the same reading dysfunction [[20](#)].

Useful additions to neuropsychological testing are semiquantitative clinician-rated instruments aiming to capture clinical changes and evaluate the impact of treatment. For example, a 5-point structured scale named the Progressive Aphasia Severity Scale (PASS) can provide a grading of the severity of impairment within a variety of speech and language domains (i.e., fluency, grammar, single-word comprehension) [21].

The variants of primary progressive aphasia

Non-fluent/agrammatic variant of primary progressive aphasia

The nvPPA is clinically characterized by two main features: an impairment of grammar and often defective motor speech production. Patients are impaired on many of the dimensions that contribute to overall fluency, as defined by classical aphasiology [22], showing an effortful and halting speech with sound errors and distortions, and/or agrammatism in language production [11, 23]. A frequent presentation is with isolated dysarthria and/or apraxia of speech (AOS). The latter, clinically characterized by a motor speech disorder with hesitancy, effortfulness with articulatory groping, phonetic errors, and dysprosody [24], owns a central role in the nvPPA presentation and is often associated with orofacial apraxia [25]. In a minority of patients, the disorder remains restricted to AOS, with no or minimal progressive impairment of language function. A recent study of a large series of patients [26] supports the existence of a spectrum of conditions characterized by AOS, ranging from “pure” forms, to patients with predominant AOS associated with nvPPA, to typical nvPPA. The qualitative features of AOS appear to be different in these conditions. Predominant distorted sound substitutions and additions with length or

complexity effect are typical of nfvPPA, while “pure” AOS and nfvPPA with predominant AOS are characterized by syllable segmentation and lengthened intersegment durations. When linguistic impairment is added to the clinical picture, omissions of grammatical words and morphemes (e.g., determiners, auxiliaries, and verbal inflections), reduced production of verbs [27, 28], incorrect argument structures, and decreased utterance length and complexity are commonly observed. Although the mean length of utterances and number of embeddings are usually reduced [14, 29, 30], reflecting a decline in ability to generate complex syntactic structures, not all mild to moderate nfvPPA patients produced syntactic errors. According to the consensus criteria, agrammatism is not required to be present if there is AOS; although these symptoms often co-occur, just one of them is necessary for the clinical diagnosis of nfvPPA [10]. While the two symptoms are usually found together, the observation of dissociated cases supports their anatomical independence [7]. Comprehension of simple declarative sentences is usually good, reflecting relatively intact single-word comprehension; on the contrary, the performance on tasks requiring the processing of complex syntactic structures, such as subordination and center embedding, is typically affected [31, 32]. While PPA patients in the early stages are usually less impaired than the typical non-fluent vascular patients with Broca's aphasia, both in terms of speech errors and syntactic structure [14], the disorder most often evolves to an aphasic picture similar to Broca's aphasia, reflecting pathologic extension to Broca's area and neighboring regions [33]. Apraxia of different kinds is clinically relevant in this subtype. Some cases show combined limb apraxia and a parkinsonian syndrome since onset [25]. These symptom complexes are suggestive of a corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP) syndromes [34, 35]. A longitudinal, voxel-based single case study of a subject with a nfvPPA onset, then developing the classical signs of CBD,

demonstrated a progression of anatomical damage from the inferior posterior frontal gyrus to the left insula and later the medial frontal lobes [36] (see [Figure 5.1](#) for an example of imaging findings in a nvPPA/CBD patient). The opposite pattern of progression has also been reported [37].

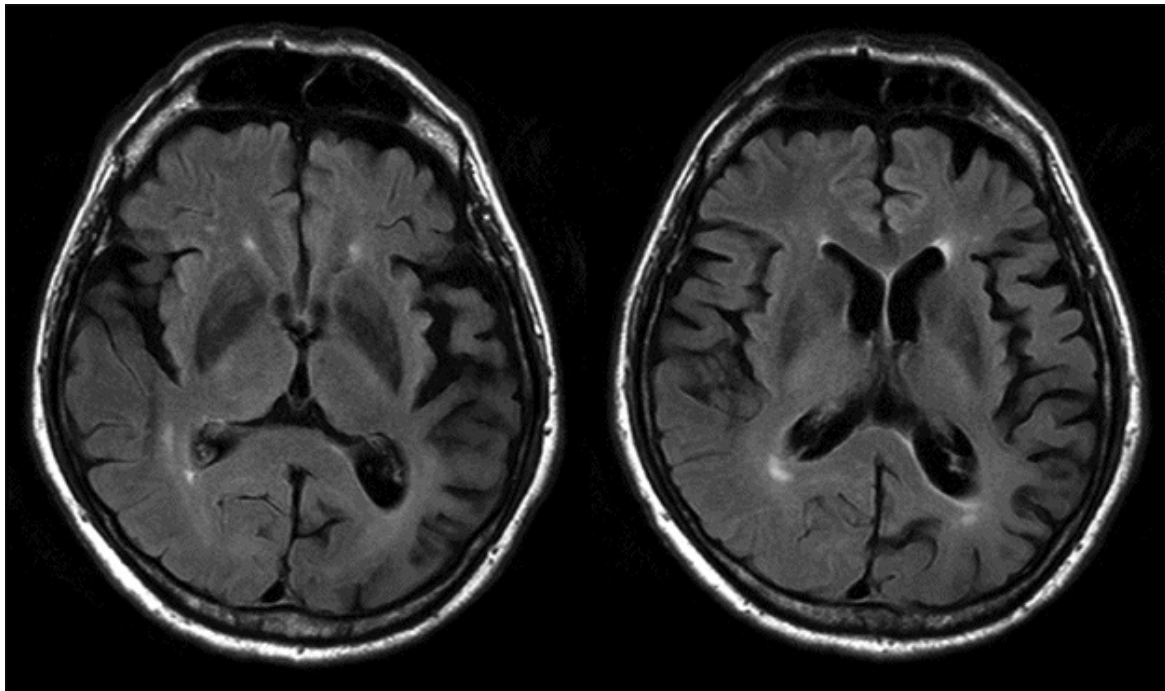


Figure 5.1 Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) scans of a 56-year-old patient affected by nvPPA, showing an enlargement of the left lateral ventricle and the frontal subarachnoid spaces bilaterally, and a widening of the left sylvian fissure resulting in a pattern of prevalent left-sided perisylvian atrophy. Images are displayed in radiologic convention (i.e., left = right; right = left).

Courtesy of Professor A. Falini, Neuroradiology – CERMAC, Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy.

The main site of cortical involvement in the nvPPA is the rolandic operculum, anterior insula, and possibly the opercular portion of Broca's area. The diagnosis of imaging-supported nvPPA indeed requires focal left-sided perisylvian region involvement, particularly of the inferior posterior frontal gyrus and insula ([Figure 5.2](#)) [10]. The primary involvement of left

inferior frontal cortex has been confirmed in recent studies using cortical thickness measures [21, 38]. [^{18}F]FDG-PET (fluorodeoxyglucose positron emission tomography) imaging studies showed also a prominent left frontal hypometabolism extending to the anterior insula [39]. Posterior perisylvian regions are increasingly impacted with disease progression [38, 40]. Moreover, frontal region damage has been proved to be mostly associated with motor speech and syntactic processes disorders, while posterior temporal region atrophy reflects phonologic errors and other types of disruption to fluency [14]. Diffusion tensor imaging studies show a pattern of reduced fractional anisotropy in the left superior longitudinal fasciculus (SLF) [41, 42]. The involvement of the “dorsal” language pathways may be responsible for disordered syntactic processing [43]. The clinical manifestations of apraxia have distinct neuroanatomical correlates: apraxia of speech with left posterior inferior frontal lobe; orofacial apraxia with left middle frontal, premotor, and supplementary motor cortical; and limb apraxia with left inferior parietal lobe damage [25, 34].

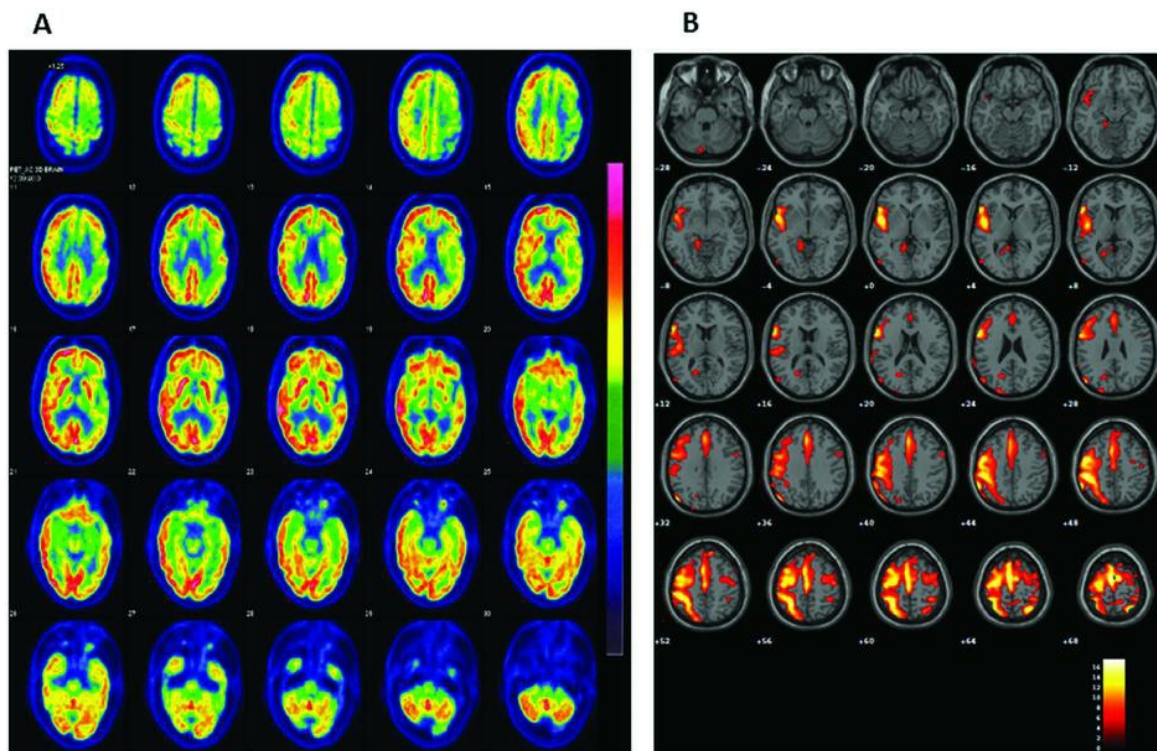


Figure 5.2 [^{18}F]FDG-PET findings in a 74-year-old man affected by nvPPA associated with corticobasal degeneration. (A) FDG-uptake distribution (displayed in radiologic convention – i.e., left = right; right = left) and (B) statistical parametric mapping (SPM-t) map of hypometabolism (displayed in neurological convention – i.e., left = left; right = right) of the single-patient [^{18}F]FDG-PET scan compared to 112 normal scans ($p = 0.05$, FWE; minimum cluster size = 100 voxels) (Della Rosa PA, Cerami C, Gallivanone F, *et al.* (2014). A standardized [^{18}F]FDG-PET template for spatial normalization in statistical parametric mapping of dementia. *Neuroinformatics*, 12(4), 575–93.), showing left frontotemporal hypometabolic pattern involving the left inferior frontal gyrus, the left insula, and bilaterally the fronto-parietal superior regions (left > right).

Courtesy of Professor D. Perani, Nuclear Medicine Department, Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy.

To summarize, the clinical presentation of nvPPA is highly heterogeneous, reflecting differences in lesion topography during disease progression [44]. The heterogeneity can be in part attributed to the variety of neuropathologic substrates associated with nvPPA. Both tau and transactive response DNA-binding protein 43 (TDP-43) pathology have been reported in autopsied cases, with a variable distribution of the two subtypes (see [45] for a review). In a recent series [9], two cases had TDP-43 type A pathology [46], while four had a tauopathy (one case of Pick's disease and three cases of CBD). Two additional patients were affected by conditions not belonging to the FTL spectrum of disorders (one prion disease and one mixed vascular/Alzheimer's pathology).

Semantic variant of primary progressive aphasia

The core features of the svPPA in the early stage are a prominent word-finding impairment in spontaneous speech, with a tendency to produce nouns

of high frequency, and severe anomia in confrontation naming tasks, with apparently preserved non-verbal semantics. The progressive semantic impairment subsequently affects single-word comprehension, and it selectively distorts intra-category differentiations leading to overgeneralized concepts [47]. As the disease progresses the impairment interferes also with inter-category discrimination, as defective single-word processing becomes clinically more severe. Impaired reading of words with irregular spelling is also typical of this subtype, and may be a consequence of semantic impairment [16]. Syntactic processing is typically spared and syntactic errors, mostly paragrammatic (substitutions of closed-class words and bound morphemes), are relatively scarce [48]. The presence of many embedded sentences in the discourse reflects attempts to cope with anomia [14]. Non-verbal skills are usually moderately affected in the early stages of the typical left-sided presentation, suggesting a prominent impairment of lexical semantics [47]. When object, people, and environmental sound identification deficits are prominent, they suggest the presence of a less common clinical presentation, associated with prominent involvement of the right anterior temporal lobe [49]. The anterior temporal lobe involvement is typically bilateral, usually more extensive in the left hemisphere [19, 36]. Preserved motor speech and syntactic function reflect the integrity of the dorsal language regions and of the corresponding white matter connections [19, 50]. The atrophy predominantly involves inferior and middle temporal gyri, anterior fusiform gyrus, amygdala and hippocampus, and entorhinal/perirhinal cortices [51–53]. Left anterior and inferior temporal atrophy accounts for the typical lexical retrieval deficits [47]. The degree of semantic memory impairment correlates with the atrophy of ventral and lateral portions of temporal lobe, while amygdala atrophy is related to emotional processing impairment [54]. Imaging findings are quite characteristic in the intermediate and advanced stages (Figure 5.3), showing

a severe “knife-edge”-type atrophy of the anterior temporal lobes with a volume loss of 50% or greater, making svPPA the easiest syndrome to diagnose on the basis of simple visual inspection. At the very beginning of disease, coronal MRI acquisitions might help to better detect the size changes of left anterior temporal lobe. Cerebral glucose metabolism is selectively reduced in the temporal lobes with a highly typical pattern of hypometabolism ([Figure 5.4](#)) [55]. As the degeneration progresses, both anterior temporal lobes as well as the ventromedial and posterior orbital frontal cortices, the insula bilaterally, and the left anterior cingulate cortex might be involved, overlapping with the imaging features of bvFTD patients [56], and accounting for the prominent behavioral symptoms that can be observed in most of these patients. In contrast to nvPPA, fractional anisotropy is mostly reduced in the “ventral” pathway, i.e., in the left inferior longitudinal fasciculus and uncinate fasciculus [41, 42, 50], rather than in the SLF/arcuate, which is affected only in its temporal component. Almost 20% of FTLD subjects showed a right temporal dominant atrophy pattern in one study [57]. While the majority of these cases (12 out of 20) presented as bvFTD, 8 subjects had a diagnosis of svPPA.

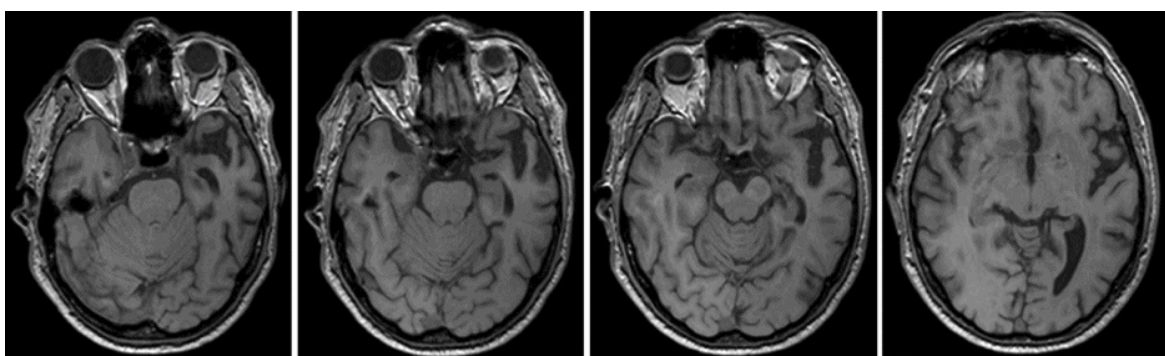


Figure 5.3 Axial T1-weighted MRI images showing a severe left temporopolar atrophy in a 58-year-old man affected by svPPA. Images are in radiologic convention (i.e., left = right; right = left).

Courtesy of Professor A. Falini, Neuroradiology – CERMAC, Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy.

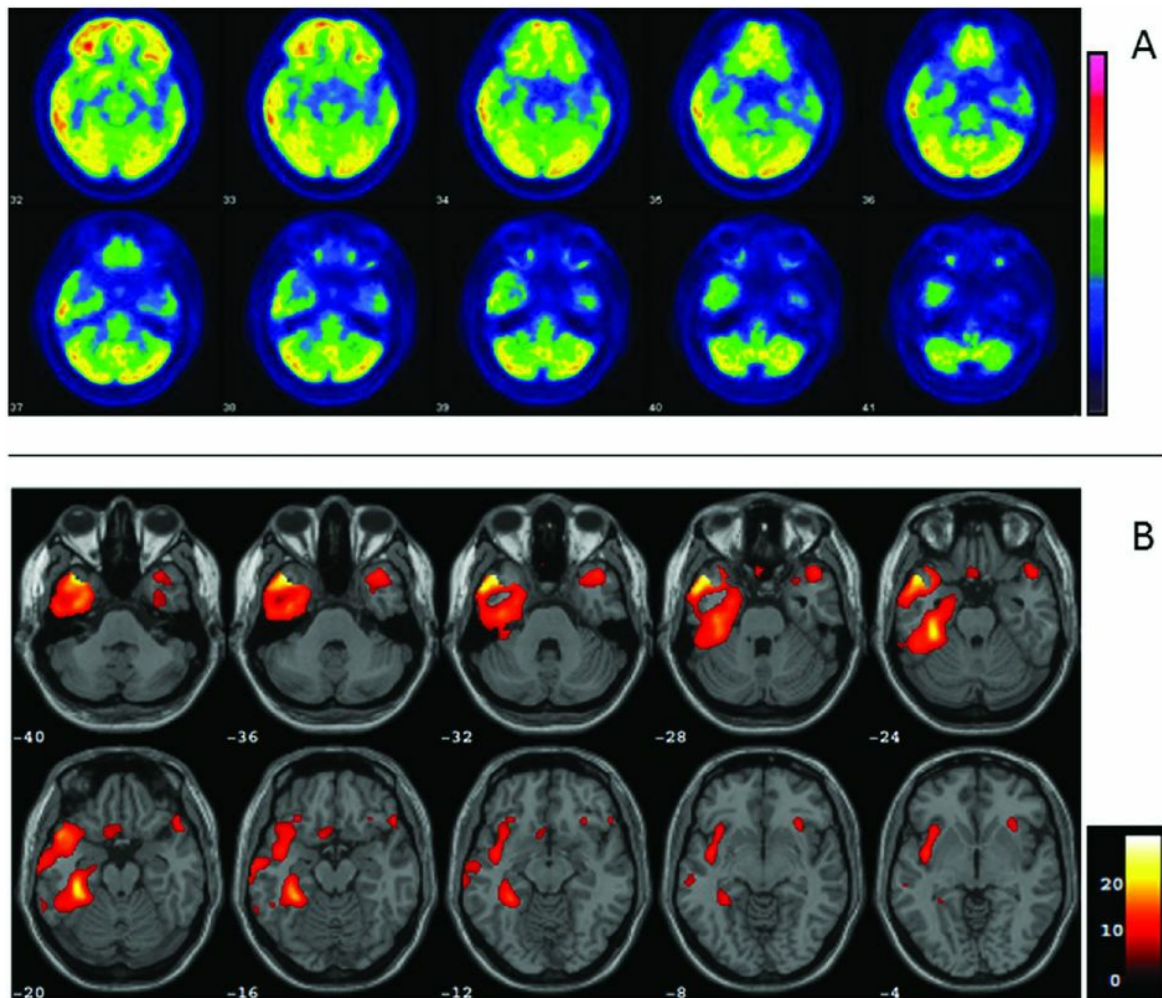


Figure 5.4 [^{18}F]FDG-PET findings in a 60-year-old man affected by svPPA. (A) FDG-uptake distribution (displayed in radiologic convention – i.e., left = right; right = left) and (B) the relative SPM-t map of hypometabolism (displayed in neurologic convention – i.e., left = left; right = right) of the single-patient [^{18}F]FDG-PET scan compared to 112 normal scans ($p = 0.05$, FWE; minimum cluster size = 100 voxels) (Della Rosa PA, Cerami C, Gallivanone F, *et al.* (2014). A standardized [^{18}F]FDG-PET template for spatial normalization in statistical parametric mapping of dementia. *Neuroinformatics*, 12(4), 575–93.), showing a pattern of involvement of temporal poles, mostly on the left side, accompanied by left orbitofrontal cortex, parahippocampal cortex, and anterior temporal regions hypometabolism.

Courtesy of Professor D. Perani, Nuclear Medicine Department, Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy.

Considerable variability in the speed of progression has been reported [58], but prognostic variables are still incompletely known. At the opposite of nvPPA cases, svPPA is characterized by a relatively homogeneous clinical picture and by consistent imaging/neuropathologic correlates. In particular, approximately 75% of cases are associated with TDP-43 pathology type C [46].

Logopenic/phonologic variant of primary progressive aphasia

This is the most recently described PPA syndrome (Table 5.1). Gorno-Tempini and colleagues reported 10 patients with slow, hesitant speech, without articulation deficits, but with many false starts, long word-finding pauses, and filled pauses and constant rewording, giving rise to an overall impression of non-fluency [11]. Impaired sentence comprehension and naming, and spared single-word comprehension and non-verbal semantics completed the clinical picture. A further analysis of the neuropsychological and imaging features of this clinical phenotype, based on an extensive cognitive assessment [59], included phonologic errors and defective repetition as further hallmarks of the syndrome. Investigation of phonologic loop functions showed that patients were severely impaired in digit, letter, and word span tasks. The performance did not improve with pointing, was influenced by word length, and did not show the normal phonologic similarity effect. These features pointed to defective phonologic memory as a crucial determinant of the clinical picture, including the impaired understanding of grammatically complex sentences [32].

Table 5.1 Core differential clinical features of the three main PPA subtypes

Articulation	Naming	Single-word comprehension	Repetition	Sy co
---------------------	---------------	--------------------------------------	-------------------	------------------

nfv	Impaired	Impaired Phonologic/phonetic errors	Preserved	Impaired	Im
sv	Normal	Impaired Semantic errors	Impaired	Preserved	Re pre
lpv	Slow, hesitant	Impaired Phonologic errors	Preserved	Impaired	Im

It is probably the case that PPA patients have been variably considered “fluent” or “non-fluent” by different researchers, depending on which aspects of fluency (e.g., speech rate, phrase length, articulatory agility, syntactic structure, and prosody) were considered. The lvPPA language production is characterized by an “intermediate” pattern of fluency, distinct from the other two variants [59]. The patients usually produce few or no errors involving speech sounds (e.g., misarticulations), whereas a subset present phonemic errors, reflecting phonologic retrieval and assembly problems, rather than motor speech impairments. Continuous rephrasing in speech production leads to phonologic paraphasias or neologisms, as seen in vascular conduction aphasia [60]. Although these patients are not agrammatic, an in-depth analysis of the connected speech has shown that they can produce paragrammatic errors [14].

Structural analyses showed a distinctive pattern of gray- and white-matter damage, involving the left posterior superior and middle temporal gyri, and inferior parietal lobule [11, 59], consistent with the hypothesis of a phonologic short-term memory impairment as the core cognitive deficit (Figure 5.5). The same pattern of damage has been shown by cortical thickness [21, 38] as well as brain metabolism studies [61, 62]. lvPPA patients have reduced fractional anisotropy largely restricted to the temporo-parietal branch of the SLF/arcuate [41, 42, 50].

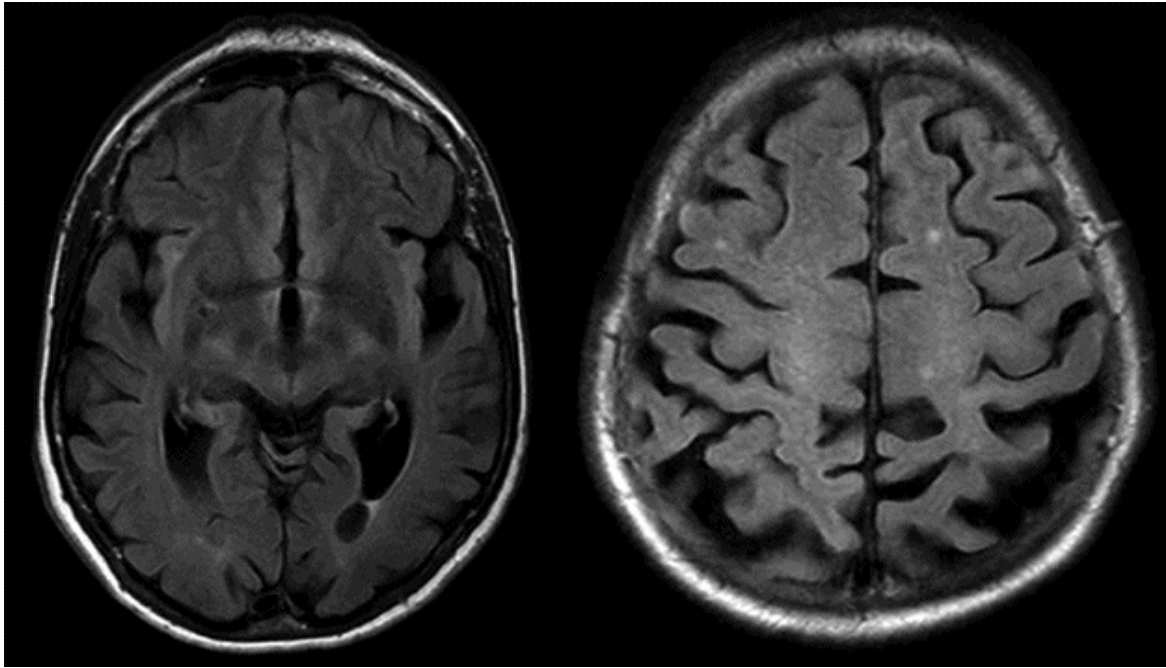


Figure 5.5 Axial T2-weighted fluid-attenuated inversion recovery (FLAIR) scans of a 65-year-old woman fulfilling criteria for lvPPA showing a bilateral widening of the sylvian fissure and the parietal subarachnoid spaces (left > right). Images are displayed in radiologic convention (i.e., left = right; right = left).

Courtesy of Professor A. Falini, Neuroradiology – CERMAC, Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy.

Recent findings show that AD is probably the most common underlying pathology of lvPPA [62, 63]. A study with [^{11}C]PiB-PET (Pittsburgh compound B-PET) and [^{18}F]FDG-PET indicated that logopenic subjects present with a higher cortical uptake of [^{11}C]PiB radioligand than patients classified with the other variants. In addition, the distribution pattern of [^{11}C]PiB-positive PPA was diffuse and comparable to those of matched AD subjects. In contrast with this diffuse pattern of [^{11}C]PiB uptake in the PiB-positive PPA cases, the location of hypometabolism on [^{18}F]FDG-PET scans reflected the features of the PPA subtypes. In particular, lvPPA subjects presented the greatest metabolic changes in the left parietal and posterolateral temporal lobes (Figure 5.6). A recent study of a large sample

of patients fulfilling the lvPPA criteria found that about one third are not positive for AD biomarkers [64]. The two thirds with probable AD pathology had a more severe clinical picture, with defective performance extending beyond language tasks and extensive involvement of the left temporo-parietal areas.

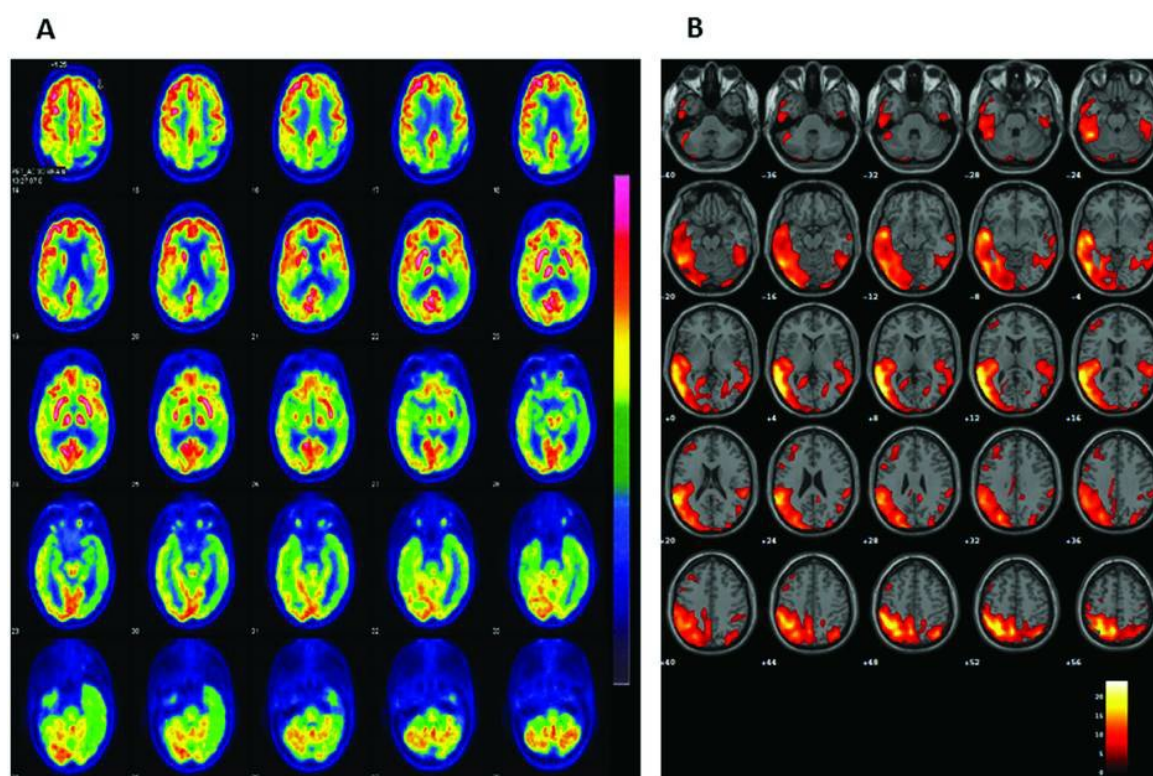


Figure 5.6 [^{18}F]FDG-PET findings in a 70-year-old man affected by lvPPA. (A) FDG-uptake distribution (displayed in radiologic convention – i.e., left = right; right = left) and (B) the relative SPM-t map of hypometabolism (displayed in neurologic convention – i.e., left = left; right = right) of the single-patient [^{18}F]FDG-PET scan compared to 112 normal scans ($p = 0.05$, FWE; minimum cluster size = 100 voxels) (Della Rosa PA, Cerami C, Gallivanone F, *et al.* (2014). A standardized [^{18}F]FDG-PET template for spatial normalization in statistical parametric mapping of dementia.

Neuroinformatics, 12(4), 575–93.), showing an involvement of superior parietal, supramarginal, angular, and superior temporal gyri, mostly on the left side.

Courtesy of Professor D. Perani, Nuclear Medicine Department, Vita-Salute

San Raffaele University and San Raffaele Scientific Institute, Milan, Italy.

The differential diagnosis with the nvPPA may be difficult, in particular in the case of patients with prominent phonologic errors, which can easily be mistaken for motor speech errors, especially in the context of decreased speech rate. This may be one of the reasons responsible for wide variations in the prevalence of this syndrome in different series [65]. The clinical picture may also have a substantial overlap with posterior cortical atrophy [66], in agreement with a common AD neuropathologic substrate. While both syndromes are considered as atypical AD presentations, the possibility of non-AD pathology should not be neglected.

Atypical and mixed cases of primary progressive aphasia

The current distinction in the three main variants, based on the most frequently observed symptom complexes, represents a gross oversimplification of the heterogeneity of the possible PPA phenotypes. Not surprisingly, variations in the location of neuropathologic damage within the large-scale language network are associated with unclassifiable, mixed clinical presentations. Among the variations, primary progressive AOS has already been mentioned [33]. Additional atypical presentations are a transcortical-type progressive aphasia, characterized by reduced speech output with preserved repetition, which is sometimes observed in the context of apathetic forms of bvFTD [44], and progressive fluent jargon aphasia, a possible evolution of the lvPPA [67]. An adynamic form of PPA has also recently been described [68].

Genetic studies

The syndromes belonging to the FTLT spectrum are often familial, and about half of cases have a positive family history [69]. Many PPA patients have a positive family history for degenerative diseases. Mutations of microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*) genes are the most frequently found genetic abnormalities, accounting for a high proportion of familial cases with autosomal dominant transmission [69].

While the most common clinical presentation associated with this *MAPT* mutation is bvFTD, the clinical phenotype is widely heterogeneous, even within the same family pedigree. PPA can infrequently be one of the possible clinical presentations, and there are a few reports of nvPPA cases carrying the *MAPT* mutation [70, 71]. The same phenotypical heterogeneity is also observed in the case of *GRN* and *C9orf72* mutations.

GRN mutations are associated with many different phenotype presentations, including PPA [72–74]. Most of these *GRN*-mutated patients present clinical features of nvPPA, but the phenotype can be atypical. Only a few single svPPA cases have been reported in association with *GRN* mutations [75, 76]. Data from the literature show a very low rate of inheritance in svPPA and lvPPA, even in studies with autopsy confirmation [58, 72, 77, 78]. A single case study described a *GRN*-mutated patient with a clinical profile closely resembling the logopenic variant, with some clinical features overlapping with the other variants [79].

More recently, FTLT cases have been reported in association with *C9orf72* mutations [80–86], with a percentage nearly comparable to *GRN* mutations [83], and a pathology characterized by the deposition of the TDP-43 protein (i.e., FTLT-TDP type A and B [46]). Some nvPPA *C9orf72*-mutated cases have been described (i.e., 6 out of 75 FTD cases of the Finnish cohort [81]). On the contrary, the association with other PPA

varieties is extremely rare. In particular, there are a few reports of svPPA cases carrying *C9orf72* mutations [76, 87].

Treatment and management

There is no effective pharmacologic treatment specifically designed for PPAs belonging to the FTL spectrum. In the case of possible AD pathology, i.e., with the lvPPA presentation, treatment with acetylcholinesterase inhibitors and memantine is usually considered as an option. There is limited published evidence about the possible role of speech and language therapy. Some anecdotal reports indicate a positive effect of treatment programs focusing on communication strategies and alternative communication methods [88, 89]. The role of patient and caregiver information cannot be underestimated. The availability of an international registry (www.ppaconnection.org) is an important resource for patients and clinicians [5].

References

1. Rogalski E, Johnson N, Weintraub S, Mesulam M. Increased frequency of learning disability in patients with primary progressive aphasia and their first-degree relatives. *Arch Neurol* 2008;**65**(2):244–8.
2. Miller ZA, Mandelli ML, Rankin KP, Henry ML, Babiak MC, Frazier DT, *et al.* Handedness and language learning disability differentially distribute in progressive aphasia variants. *Brain* 2013;**136**(Pt 11):3461–73.
3. Luzzatti C, Poeck K. An early description of slowly progressive aphasia. *Arch Neurol* 1991;**48**(2):228–9.

-
4. Mesulam MM. Slowly progressive aphasia without generalized dementia. *Ann Neurol* 1982;**11**:592–8.

 5. Mesulam MM. Primary progressive aphasia and the language network: the 2013 H. Houston Merritt Lecture. *Neurology* 2013;**81**(5):456–62.

 6. Mesulam MM. Primary progressive aphasia. *Ann Neurol* 2001;**49**(4):425–32.

 7. Mesulam MM, Wieneke C, Thompson C, Rogalski E, Weintraub S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain* 2012;**135**(Pt 5):1537–53.

 8. Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. *CNS Drugs* 2010;**24**(5):375–98.

 9. Harris JM, Gall C, Thompson JC, Richardson AM, Neary D, du Plessis D, *et al*. Classification and pathology of primary progressive aphasia. *Neurology* 2013;**81**(21):1832–9.

 10. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, *et al*. Classification of primary progressive aphasia and its variants. *Neurology* 2011;**76**(11):1006–14.

 11. Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, *et al*. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol* 2004;**55**:335–46.

 12. Cappa SF, Gorno-Tempini ML. Clinical phenotypes of progressive aphasia. *Fut Neurol* 2009;**4**:153–60.

 13. Kertesz A. *Western Aphasia Battery* New York: Grune and Stratton; 1982.

 14. Wilson SM, Henry ML, Besbris M, Ogar JM, Dronkers NF, Jarrold W, *et al*. Connected speech production in three variants of primary progressive aphasia. *Brain* 2010;**133**(Pt 7):2069–88.

-
- 15.** Weintraub S, Mesulam MM, Wieneke C, Rademaker A, Rogalski EJ, Thompson CK. The northwestern anagram test: measuring sentence production in primary progressive aphasia. *Am J Alzheimers Dis Other Dement* 2009;**24**(5):408–16.
-
- 16.** Hodges JR, Graham N, Patterson K. Charting the progression in semantic dementia: implications for the organisation of semantic memory. *Memory* 1995;**3**(3–4):463–95.
-
- 17.** Catricala E, Della Rosa PA, Ginex V, Mussetti Z, Plebani V, Cappa SF. An Italian battery for the assessment of semantic memory disorders. *Neurol Sci* 2013;**34**(6):985–93.
-
- 18.** Wilson SM, Galantucci S, Tartaglia MC, Gorno-Tempini ML. The neural basis of syntactic deficits in primary progressive aphasia. *Brain Lang* 2012;**122**(3):190–8.
-
- 19.** Wilson SM, Brambati SM, Henry RG, Handwerker DA, Agosta F, Miller BL, *et al.* The neural basis of surface dyslexia in semantic dementia. *Brain* 2009;**132**(Pt 1):71–86.
-
- 20.** Rozzini L, Bianchetti A, Lussignoli G, Cappa SF, Trabucchi M. Surface dyslexia in an Italian patient with semantic dementia. *Neurocase* 1997;**3**:307–12.
-
- 21.** Sapolsky D, Bakkour A, Negreira A, Nalipinski P, Weintraub S, Mesulam MM, *et al.* Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia. *Neurology* 2010;**75**(4):358–66.
-
- 22.** Goodglass H, Kaplan E. *Assessment of Aphasia and Related Disorders* Philadelphia: Lea & Febiger; 1983.
-
- 23.** Hodges JR, Patterson K. Nonfluent progressive aphasia and semantic dementia: a comparative neuropsychological study. *J Int Neuropsychol Soc* 1996;**2**(6):511–24.
-

-
- 24.** Ogar J, Slama H, Dronkers N, Amici S, Gorno-Tempini ML. Apraxia of speech: an overview. *Neurocase* 2005;**11**(6):427–32.
-
- 25.** Rohrer JD, Rossor MN, Warren JD. Apraxia in progressive nonfluent aphasia. *J Neurol* 2010;**257**(4):569–74.
-
- 26.** Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Lowe VJ, *et al.* Syndromes dominated by apraxia of speech show distinct characteristics from agrammatic PPA. *Neurology* 2013;**81**(4):337–45.
-
- 27.** Hillis AE, Oh S, Ken L. Deterioration of naming nouns versus verbs in primary progressive aphasia. *Ann Neurol* 2004;**55**(2):268–75.
-
- 28.** Cotelli M, Borroni B, Manenti R, Alberici A, Calabria M, Agosti C, *et al.* Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. *Neuropsychology* 2006;**20**(5):558–65.
-
- 29.** Ash S, Moore P, Antani S, McCawley G, Work M, Grossman M. Trying to tell a tale: discourse impairments in progressive aphasia and frontotemporal dementia. *Neurology* 2006;**66**(9):1405–13.
-
- 30.** Ash S, Evans E, O'Shea J, Powers J, Boller A, Weinberg D, *et al.* Differentiating primary progressive aphasia in a brief sample of connected speech. *Neurology* 2013;**81**(4):329–36.
-
- 31.** Grossman M, Mickanin J, Onishi K, Hughes E, D'Esposito M, Ding XS, *et al.* Progressive nonfluent aphasia: language, cognitive, and PET measures contrasted with probable Alzheimer's disease. *J Cogn Neurosci* 1996;**8**(2):135–54.
-
- 32.** Charles D, Olm C, Powers J, Ash S, Irwin DJ, McMillan CT, *et al.* Grammatical comprehension deficits in non-fluent/agrammatic primary progressive aphasia. *J Neurol Neurosurg Psychiatry* 2014;**85**(3):249–56.
-
- 33.** Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Master AV,

et al. Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. *Brain* 2012;**135**(Pt 5):1522–36.

34. Josephs KA, Duffy JR, Strand EA, Whitwell JL, Layton KF, Parisi JE, *et al.* Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain* 2006;**129**(Pt 6):1385–98.

35. Josephs KA, Duffy JR. Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy. *Curr Opin Neurol* 2008;**21**(6):688–92.

36. Gorno-Tempini ML, Murray RC, Rankin KP, Weiner MW, Miller BL. Clinical, cognitive and anatomical evolution from nonfluent progressive aphasia to corticobasal syndrome: a case report. *Neurocase* 2004;**10**(6):426–36.

37. Kertesz A, Martinez-Lage P, Davidson W, Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. *Neurology* 2000;**55**(9):1368–75.

38. Rogalski E, Cobia D, Harrison TM, Wieneke C, Weintraub S, Mesulam MM. Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. *Neurology* 2011;**76**(21):1804–10.

39. Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. *Brain* 2003;**126**(Pt 11):2406–18.

40. Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, Rossor MN, *et al.* Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology* 2009;**72**(18):1562–9.

41. Galantucci S, Tartaglia MC, Wilson SM, Henry ML, Filippi M, Agosta F, *et al.* White matter damage in primary progressive aphasia: a diffusion tensor tractography study. *Brain* 2011;**134**(Pt 10):3011–29.

-
- 42.** Whitwell JL, Avula R, Senjem ML, Kantarci K, Weigand SD, Samikoglu A, *et al.* Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia. *Neurology* 2010;**74**(16):1279–87.
-
- 43.** Wilson SM, Galantucci S, Tartaglia MC, Rising K, Patterson DK, Henry ML, *et al.* Syntactic processing depends on dorsal language tracts. *Neuron* 2011;**72**(2):397–403.
-
- 44.** Cappa SF, Perani D, Messa C, Miozzo A, Fazio F. Varieties of progressive non-fluent aphasia. *Ann N Y Acad Sci* 1996;**777**:243–8.
-
- 45.** Grossman M. The non-fluent/agrammatic variant of primary progressive aphasia. *Lancet Neurol* 2012;**11**(6):545–55.
-
- 46.** Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, *et al.* A harmonized classification system for FTLN-TDP pathology. *Acta Neuropathol* 2011;**122**(1):111–13.
-
- 47.** Mesulam MM, Wieneke C, Hurley R, Rademaker A, Thompson CK, Weintraub S, *et al.* Words and objects at the tip of the left temporal lobe in primary progressive aphasia. *Brain* 2013;**139**(Pt 2):601–18.
-
- 48.** Meteyard L, Patterson K. The relation between content and structure in language production: an analysis of speech errors in semantic dementia. *Brain Lang* 2009;**110**(3):121–34.
-
- 49.** Gainotti G. Why are the right and left hemisphere conceptual representations different? *Behav Neurol* 2014;**2014**:603134.
-
- 50.** Agosta F, Henry RG, Migliaccio R, Neuhaus J, Miller BL, Dronkers NF, *et al.* Language networks in semantic dementia. *Brain* 2010;**133**(Pt 1):286–99.
-
- 51.** Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RSJ, Hodges JR. A voxel-based morphometry study of semantic dementia:

relationship between temporal lobe atrophy and semantic dementia. *Ann Neurol* 2000;**47**:36–45.

52. Galton CJ, Patterson K, Graham K, Lambon-Ralph MA, Williams G, Antoun N, *et al.* Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 2001;**57**(2):216–25.

53. Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, *et al.* Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol* 2001;**49**(4):433–42.

54. Rosen HJ, Allison SC, Ogar JM, Amici S, Rose K, Dronkers N, *et al.* Behavioral features in semantic dementia vs other forms of progressive aphasia. *Neurology* 2006;**67**(10):1752–6.

55. Diehl J, Grimmer T, Drzezga A, Riemenschneider M, Forstl H, Kurz A. Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiol Aging* 2004;**25**(8):1051–6.

56. Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, *et al.* Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* 2002;**58**(2):198–208.

57. Josephs KA, Whitwell JL, Knopman DS, Boeve BF, Vemuri P, Senjem ML, *et al.* Two distinct subtypes of right temporal variant frontotemporal dementia. *Neurology* 2009;**73**(18):1443–50.

58. Hodges JR, Mitchell J, Dawson K, Spillantini MG, Xuereb JH, McMonagle P, *et al.* Semantic dementia: demography, familial factors and survival in a consecutive series of 100 cases. *Brain* 2010;**133**(Pt 1):300–6.

59. Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, *et al.* The logopenic/phonological variant of primary progressive aphasia. *Neurology* 2008;**71**(16):1227–34.

-
- 60.** Kohn SE. *Conduction Aphasia* Hillsdale: Lawrence Erlbaum Associates; 1992.
-
- 61.** Josephs KA, Duffy JR, Fossett TR, Strand EA, Claassen DO, Whitwell JL, *et al.* Fluorodeoxyglucose F18 positron emission tomography in progressive apraxia of speech and primary progressive aphasia variants. *Arch Neurol* 2010;**67**(5):596–605.
-
- 62.** Rabinovici GD, Jagust WJ, Furst AJ, Ogar JM, Racine CA, Mormino EC, *et al.* Aβ amyloid and glucose metabolism in three variants of primary progressive aphasia. *Ann Neurol* 2008;**64**(4):388–401.
-
- 63.** Mesulam M, Wicklund A, Johnson N, Rogalski E, Léger GC, Rademaker A, *et al.* Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Ann Neurol* 2008;**63**(6):709–19.
-
- 64.** Teichmann M, Kas A, Boutet C, Ferrieux S, Nogues M, Samri D, *et al.* Deciphering logopenic primary progressive aphasia: a clinical, imaging and biomarker investigation. *Brain* 2013;**136**(Pt 11):3474–88.
-
- 65.** Sajjadi SA, Patterson K, Arnold RJ, Watson PC, Nestor PJ. Primary progressive aphasia: a tale of two syndromes and the rest. *Neurology* 2012;**78**(21):1670–7.
-
- 66.** Rohrer JD, Rossor MN, Warren JD. Alzheimer's pathology in primary progressive aphasia. *Neurobiol Aging* 2012;**33**(4):744–52.
-
- 67.** Caffarra P, Gardini S, Cappa S, Dieci F, Concari L, Barocco F, *et al.* Degenerative jargon aphasia: unusual progression of logopenic/phonological progressive aphasia? *Behav Neurol* 2013;**26**(1–2):89–93.
-
- 68.** Perez DL, Dickerson BC, McGinnis SM, Sapolsky D, Johnson K, Searl M, *et al.* You don't say: dynamic aphasia, another variant of primary progressive aphasia? *J Alzheimers Dis* 2013;**34**(1):139–44.
-

-
- 69.** Cerami C, Scarpini E, Cappa SF, Galimberti D. Frontotemporal lobar degeneration: current knowledge and future challenges. *J Neurol* 2012;**259**(11):2278–86.
-
- 70.** Villa C, Ghezzi L, Pietroboni AM, Fenoglio C, Cortini F, Serpente M, *et al.* A novel MAPT mutation associated with the clinical phenotype of progressive nonfluent aphasia. *J Alzheimers Dis* 2011;**26**(1):19–26.
-
- 71.** Lee SE, Tartaglia MC, Yener G, Genc S, Seeley WW, Sanchez-Juan P, *et al.* Neurodegenerative disease phenotypes in carriers of MAPT p.A152T, a risk factor for frontotemporal dementia spectrum disorders and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2013;**27**(4):302–9.
-
- 72.** Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, *et al.* The heritability and genetics of frontotemporal lobar degeneration. *Neurology* 2009;**73**(18):1451–6.
-
- 73.** Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. *J Neurol Neurosurg Psychiatry* 2011;**82**(5):476–86.
-
- 74.** van der Zee J, Rademakers R, Engelborghs S, Gijssels I, Bogaerts V, Vandenberghe R, *et al.* A Belgian ancestral haplotype harbours a highly prevalent mutation for 17q21-linked tau-negative FTLTD. *Brain* 2006;**129**(Pt 4):841–52.
-
- 75.** Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, *et al.* Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain* 2008;**131**(Pt 3):732–46.
-
- 76.** Cerami C, Marcone A, Galimberti D, Villa C, Fenoglio C, Scarpini E, *et al.* Novel missense progranulin gene mutation associated with the semantic variant of primary progressive aphasia. *J Alzheimers Dis* 2013;**36**(3):415–20.
-
- 77.** Seelaar H, Kamphorst W, Rosso SM, Azmani A, Masdjedi R, de Koning I,

et al. Distinct genetic forms of frontotemporal dementia. *Neurology* 2008;**71**(16):1220–6.

78. Goldman JS, Farmer JM, Wood EM, Johnson JK, Boxer A, Neuhaus J, *et al.* Comparison of family histories in FTLD subtypes and related tauopathies. *Neurology* 2005;**65**(11):1817–19.

79. Rohrer JD, Crutch SJ, Warrington EK, Warren JD. Progranulin-associated primary progressive aphasia: a distinct phenotype? *Neuropsychologia* 2010;**48**(1):288–97.

80. Calvo A, Moglia C, Canosa A, Cistaro A, Valentini C, Carrara G, *et al.* Amyotrophic lateral sclerosis/frontotemporal dementia with predominant manifestations of obsessive-compulsive disorder associated to GGGGCC expansion of the *c9orf72* gene. *J Neurol* 2012;**259**(12):2723–5.

81. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS and FTD. *Neuron* 2011;**72**(2):257–68.

82. DeJesus-Hernandez M, Desaro P, Johnston A, Ross OA, Wszolek ZK, Ertekin-Taner N, *et al.* Novel p.Ile151Val mutation in VCP in a patient of African American descent with sporadic ALS. *Neurology* 2011;**77**(11):1102–3.

83. Gijselinck I, Van Langenhove T, van der Zee J, Sleegers K, Philtjens S, Kleinberger G, *et al.* A *C9orf72* promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. *Lancet Neurol* 2012;**11**(1):54–65.

84. Dobson-Stone C, Hallupp M, Bartley L, Shepherd CE, Halliday GM, Schofield PR, *et al.* *C9ORF72* repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. *Neurology* 2012;**79**(10):995–1001.

85. Galimberti D, Fenoglio C, Serpente M, Villa C, Bonsi R, Arighi A, *et al.*

Autosomal dominant frontotempo-ral lobar degeneration due to the *C9ORF72* hexanucleotide repeat expansion: late-onset psychotic clinical presentation. *Biol Psychiatry* 2013;**74**(5):384–91.

86. Cerami C, Marcone A, Galimberti D, Zamboni M, Fenoglio C, Serpente M, *et al.* Novel evidence of phenotypical variability in the hexanucleotide repeat expansion in chromosome 9. *J Alzheimers Dis* 2013;**35**(3):455–62.

87. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, *et al.* Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations. *Brain* 2012;**135**(Pt 3):693–708.

88. Farrajota L, Maruta C, Maroco J, Martins IP, Guerreiro M, de Mendonca A. Speech therapy in primary progressive aphasia: a pilot study. *Dement Geriatr Cogn Dis Extra* 2012;**2**(1):321–31.

89. Henry ML, Meese MV, Truong S, Babiak MC, Miller BL, Gorno-Tempini ML. Treatment for apraxia of speech in nonfluent variant primary progressive aphasia. *Behav Neurol* 2013;**26**(1–2):77–88.

Chapter 6

The FTD-ALS spectrum



Thomas H. Bak and Sharon Abrahams

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

FTD-ALS spectrum: the evolution of the concept

The current wave of interest in the relationship between frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) could lead to the impression that an association between both diseases is a relatively recent finding. In fact, the observation of an overlap between FTD and ALS is among the earliest and most well-documented combinations of two neurodegenerative diseases. Cognitive and behavioral symptoms in ALS were regularly reported since the late nineteenth century and an explicit link between FTD (at that time referred to as Pick's disease) and ALS was made by Anton von Braunmühl in 1932 (for a historical overview see [\[1\]](#)).

These early reports show a characteristic geographic and temporal pattern, which could shed light on some current debates in the field. Most

early descriptions of ALS patients demonstrating aphasia, dementia, personality change, behavioral symptoms, or psychosis came mainly from continental central Europe and Japan (i.e., from countries where neurology and psychiatry were considered at that time to be two complementary aspects of the same medical specialty in a way in which obstetrics and gynecology might still be viewed today). Hence, the same specialists were seeing patients with psychiatric and neurologic disorders and paid attention to both types of symptoms and signs in their history taking and examination. With time, they observed a number of patients who presented with changes in language, cognition, or behavior and later developed signs of motor neuron disease (MND) such as weakness, wasting, and fasciculations. They recognized these different types of symptoms as being related and speculated about the underlying pathology. The situation was (and often still is) different in Britain and other English-speaking countries, where neurology and psychiatry tend to be separated. A neurologist who diagnoses ALS might not be aware of the psychiatric past history and the patients and their family are not likely to mention it spontaneously, so it can go unnoticed. Such differences in approach to patients with ALS might explain some of the recent controversies, such as the current debate about the presence of psychotic symptoms in patients with ALS [2], in particular in those with the *C9orf72* gene mutation [3]. Since in most cases psychotic symptoms predate the development of motor signs by months or even years [4–6], they are easily missed unless they have been witnessed by the same practitioner who later diagnoses ALS or are specifically explored in the interview.

Although the idea of ALS as a purely motor syndrome remained predominant in the English-speaking world until the beginning of the twenty-first century, reports of cognitive and behavioral changes in ALS became more frequent after 1945, possibly under the influence of physicians who

had emigrated to the UK and USA from Europe, particularly from German-speaking countries. In 1981, Hudson challenged the exclusively motor character of ALS in his seminal review of ALS-associated dementia and parkinsonism [7]. Thanks to discussions with his foreign colleagues working at this time with him in Toronto, Hudson was aware of the substantial amount of literature published on this topic in German, Japanese, and other languages and has reviewed it in his paper (Hudson, personal communication). However, Hudson's paper did not provide details about the characteristics of the dementia; at that time dementia was widely regarded as a unitary syndrome.

This changed in the last decades of the twentieth century with the growing recognition of the differences in clinical presentation and underlying pathology between Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, and other types of dementia. The cognitive and behavioral changes in ALS were found to resemble those seen in FTD and FTD-MND was proposed as a diagnostic category [8]. Within the FTD spectrum, a further distinction was made between the behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA). bvFTD (sometimes referred to as the frontal variant FTD) is characterized clinically by personality change, inappropriate and often disinhibited behavior, executive dysfunction, deficits in social abilities, and lack of insight with pathology predominantly affecting orbitofrontal and nearby regions [9]. The progressive aphasia were more heterogeneous, encompassing originally two major diagnostic categories: progressive non-fluent aphasia (PNFA) and semantic dementia (SD), and later extended to encompass logopenic aphasia [10]. While the notion of FTD-MND became widely accepted, it remained less clear to which of the FTD subtypes it was best linked [1]. Most reports stressed the executive symptoms and

personality changes, the pathognomonic features of bvFTD. Language changes tended to remain in their shadow.

By the year 2000, the evidence in favor of an overlap between FTD and ALS was overwhelming [11]. However, most of it was based on clinical observation. This was to change dramatically in the next decade with advances in molecular pathology and genetics. The discovery of the importance of ubiquitin and transactive response DNA-binding protein 43 (TDP-43) in the pathology of ALS as well as that of FTD brought both diseases closer together also on the molecular level [12]. The identification of the *C9orf72* gene [13, 14] generated great interest in basic pathologic mechanisms underlying both conditions as well as in a better characterization of the clinical presentation of patients with this mutation [3]. The FTD-ALS overlap has since become one of the most researched and hotly debated topics in neurodegeneration. Consequently, the most important issues to be addressed have changed. Now, instead of questioning the existence of an overlap between FTD and ALS the field is focused on the nature of its overlap in terms of clinical presentation and underlying pathology. The two crucial and interlinked questions arising in this context are: (1) Is FTD-ALS a simple overlap of FTD and ALS, combining to a varying extent features of both diseases, or does it have its own specific characteristics, distinguishing it from the classical forms of FTD and ALS?; and (2) Are there any meaningful subgroups within the FTD-ALS spectrum, clinically or pathologically?

In terms of the first question, the predominant view until recently was that of a continuum, with pure ALS and FTD being the polar phenotypes [15, 16]. However, recently, an alternative idea has been put forward: that of FTD-ALS as a distinct nosologic entity, combining to a certain extent features of the classical FTD and ALS, but also displaying its own characteristics [1]. Two features of FTD-ALS which are particularly

difficult to accommodate in the simple continuum theory are psychotic symptoms and language changes [2]. Both will be discussed below.

Regarding the second question, it is recognized that cognitive and behavioral changes in ALS can occur separately as proposed in the consensus diagnostic criteria [17]. More recently, Taylor *et al.* demonstrated that language impairment and executive dysfunction do not always overlap [18]. Moreover, different genetic variants of ALS might be characterized by different cognitive profiles. The *SOD1* mutation, the first ALS-related mutation discovered, interestingly is associated with preserved cognitive function, apart from a mild deficit in naming [19]. In contrast, the *C9orf72* and *OPTN* mutations seem to be characterized by extensive cognitive dysfunction, as will be described when discussing the genetic aspects of FTD-ALS. Finally, although this chapter focuses on ALS as the most common form of MND, cognitive deficits have also been documented in other forms of MND such as primary lateral sclerosis (PLS) [20, 21] and progressive muscular atrophy (PMA) [22], although in the latter the evidence so far is inconclusive [23]. More data will be needed before we can draw conclusions about the specific patterns of cognitive and behavioral changes in these syndromes.

Profile of cognitive change in FTD-ALS

Over the last 15–20 years, an influx of publications has consistently demonstrated that up to 50% of ALS patients show some form of cognitive impairment (for review see [24]). The prevalence of FTD varies, with 3–5% cited by earlier studies [25] but as much as 15% using more recent FTD diagnostic criteria which focus on behavior change [26]. The remaining ~35% of ALS patients with cognitive change do not have a full-blown

dementia syndrome but have specific cognitive deficits on neuropsychological testing (e.g., [27]). These estimates are confirmed by population-based studies using incident sampling methods [28].

Cognitive research in ALS patients has tended to employ assessment of standard and some experimental neuropsychological techniques and has revealed a specific profile of selective cognitive change. This profile is characterized by a predominant pattern of executive dysfunction in non-demented ALS patients [29] while more recent studies have highlighted the heterogeneity of impairments with the presence of language dysfunction [18] and deficits in social cognition. A meta-analysis confirmed evidence of deficits in multiple domains [30].

A consensus criteria set for diagnosing frontotemporal cognitive-behavioral syndromes in ALS has been proposed [17]. This consortium recommends classification of patients with a frontotemporal cognitive-behavioral syndrome into three subgroups: (1) ALS-FTD (using the three variants of bvFTD, PNFA, and SD), (2) ALS with cognitive impairment (ALSci), and (3) ALS with behavioral impairment (ALSbi). To be classified as ALSci patients must undergo full neuropsychological assessment and demonstrate impairment (as defined by < 5th percentile against published age- and education-matched normative data) on two separate tests of executive functions. It recommends that other domains should be assessed, yet the results in these domains do not affect classification. Furthermore, background characteristics which need to be taken into account with the interpretation of scores include the presence of a psychiatric condition, psychological reaction to the diagnosis, premorbid diagnosis of personality disorder, and emotional lability. To be classified as ALSbi patients must show at least two non-overlapping supportive diagnostic features from the standard diagnostic criteria for bvFTD. Evidence should be obtained from at least two sources such as observation

or structured interview/questionnaire and must include a carer report. Furthermore, the clinician should clarify that the changes are new and cannot be accounted for by physical disability. The limitations of these criteria have been highlighted by Goldstein and Abrahams [24], who have suggested that assessing executive dysfunction alone may underestimate the prevalence of cognitive impairment, given in particular the recent findings of high rates of language dysfunction in an ALS population. Furthermore, patients can have both behavioral and cognitive changes with considerable overlap between ALSci and ALSbi classifications. Following the 2013 International ALS-FTD Symposium in London, Ontario, Canada, hosted by Professor Michael Strong, modifications to the criteria were discussed for future publication.

The study of the longitudinal course of cognitive change in ALS has been challenging owing to increasing disability and high attrition rates. Some studies have shown evidence of progressive cognitive deterioration while others have not [31]. In an extensive prospective study of 186 Irish patients, cognitive decline was found to be more rapid in those with cognitive impairment at baseline, while those who were cognitively intact at baseline tended to remain that way [32]. Analysis of survival rates has indicated that a frontotemporal cognitive-behavioral syndrome is a negative prognostic factor, whether this be FTD [33] or executive dysfunction [34], although it remains unclear whether this is due to severity of disease course or adherence to intervention.

Executive dysfunction in FTD-ALS

Executive dysfunction has been highlighted as the most typical impairment in patients with ALS [29], which has been confirmed by recent population-

based studies [28]. The most striking and consistently reported deficit in neuropsychological studies is in verbal fluency and most commonly letter or phonemic fluency [29, 35, 36]. Assessment of fluency for ALS patients with varying disability can be problematic because of difficulties writing or speaking. This has necessitated the development of the verbal fluency index in which following word generation, the patient is timed as they either copy (written fluency) or read (spoken fluency) the words again, providing an estimation of motor speed [37]. From this the verbal fluency index is calculated, which consists of the average time taken to *think* of the word (see [Figure 6.1](#)). Using this method, a deficit has been demonstrated repeatedly across studies and which is not caused or exaggerated by physical disability. Further investigation of the cognitive underpinnings of this impairment revealed that poor performance was primarily caused by executive dysfunction and not problems in working memory (in terms of abnormalities of the phonologic store or articulatory rehearsal loop) or in simple word retrieval involved in naming [29]. Letter fluency is reliant on processes of initiation, strategy formation, set-shifting, sustained attention, and inhibition. Verbal fluency impairments have also been shown to occur early in the course of the disease [31], and to correlate with eye movement abnormalities (ocular fixation) as a neurologic examination marker of frontal lobe dysfunction [38]. They have been found to be more prominent in patients with pseudobulbar palsy although not restricted to these patients [35], and are absent in some familial forms of the disease [19] and in those with progressive muscular atrophy [23].

$$\text{Verbal fluency index (Vfi)} = \frac{\text{Total time for test} - \text{Time to copy or read words generated}}{\text{Number of words generated}}$$

Figure 6.1 Calculation of verbal fluency index. The verbal fluency index (Vfi) is calculated using a motor control condition in which after the participant has generated words in the given time (e.g., one minute to generate words beginning with a given letter), they are then asked to copy out or read aloud the words they have previously generated as fast as possible. This gives a measure of motor speed. The total time for the test minus the measure of motor speed is then divided by the number of words produced to give an estimation of the average time taken to “think” of each word or Vfi.

Executive dysfunction has been revealed on a range of tests including tests of attention monitoring and switching, rule deduction, cognitive flexibility, such as the Wisconsin Card Sorting or Trail Making Tests [35, 36, 39], and on other measures of concept formation (Delis–Kaplan Executive Function System Sorting Test), with poor performance in some ALS patients which was related to reduced verbal fluency [40]. Furthermore, deficits have also been revealed on tests dependent on the manipulations of concepts in working memory, such as reverse digit span or the N-back task. Impairments have also recently been shown using dual-task paradigms [41]. This procedure is thought to tap functions of the central executive component of working memory by performing two tasks concurrently (in this case a visual processing speed task and digit recall).

Of note patients did not show slowed processing speed using a visual inspection time task in which stimulus presentation times were altered and which was therefore independent of motor speed. Thus, this study demonstrated executive dysfunction without generalized cognitive slowing.

The neuropsychological literature demonstrates that most of these executive functions are mediated by dorsolateral prefrontal cortex (see imaging section for further support). However other functions that are more dependent on orbitomedial prefrontal processes are now the focus of investigation. Patients have been shown to have abnormal risk-taking behavior on the Iowa Gambling Task with a failure to learn to avoid high-risk choices of decks of cards on the basis of monetary rewards or punishments [42]. Other studies have employed tasks which purportedly are more ecologically valid than traditional tests of executive functions in an attempt to relate dysfunction to everyday life. Deficits in ALS patients have been shown using the Medication Scheduling Task [43] and the Holiday Apartment Task [44] with patients showing difficulties in reasoning and coordinating rules. The latter consists of a non-risk decision-making task which involves mental heuristics. ALS patients' strategy use on this task appeared akin to that of patients with damage of the ventromedial prefrontal cortex and not those with dorsolateral prefrontal dysfunction.

Language dysfunction in FTD-ALS

Although language symptoms were frequently discussed in early description of ALS [1], they were generally considered, until the seminal paper by Caselli *et al.* [45], to play only a marginal role in the disease. One of the biggest problems impeding the study of language in ALS is the fact that a large proportion of patients present with dysarthria or dysphonia as a

consequence of the involvement of speech-controlling muscles. Hence, the dramatic reduction in speech output seen in many ALS patients tended to be attributed to a peripheral impairment rather than to a central involvement of the faculty of language. Furthermore, formal language assessment was rarely conducted.

Advances in our understanding of the language impairments in ALS came from two directions. One was the study of language comprehension. Tests using tasks such as pointing to a picture allowed researchers to examine the understanding of single words as well as full sentences even in patients with practically absent spontaneous speech output. The emerging evidence from this work highlighted not only pronounced difficulty in understanding grammatically complex sentences but also a less expected deficit in the comprehension of single words, particularly verbs [46]. Since then, deficits in the processing of verbs and also the underlying concepts of actions have become one of the most consistently documented linguistic features of ALS [47–49] and have been associated with characteristic pathologic changes in Brodmann areas 44 and 45 (Broca's area) [4]. Indeed, ALS has come to be regarded as a prototypical “lesion example” illustrating theories of embodied cognition [50, 51].

The second area which proved particularly fruitful in ALS research is the analysis of written language. Like the tests of comprehension based on pointing rather than speaking, written language can be studied also in patients with severe dysarthria or even mutism. As in language comprehension, the examination of written language has unearthed impairment at the single-word as well as sentence level [4]. A pioneering work in this field was conducted by Japanese authors who demonstrated that ALS patients tend to have more problems with the phonologic kana than with the semantically related kanji script [52]. This is remarkable since kana is visually much simpler, has fewer characters, and is acquired earlier

developmentally than kanji. One would expect, therefore, that kana would be more resistant to brain pathology than the more complex kanji. The reason for this has not yet been determined, but interestingly spelling errors have now also been documented in English-speaking patients [53].

Considering these two areas of language comprehension and written language, it is not surprising that language impairment has been so long overlooked in ALS. The most common test of language functions in clinical practice, picture naming, is of limited value in ALS patients. First, it relies on speech production, which, as was mentioned before, is often reduced or even absent. Second, the vast majority of naming tests use only pictures of objects, and hence are not able to detect deficit in verb processing characteristic for ALS. Accordingly, a recent study using a much wider range of language tasks than most previous ones estimated that language dysfunction might constitute the most common cognitive deficit in ALS patients, even more common than executive dysfunction [18, 54]. In practical terms, comprehension of verbs as well as spelling are now part of a new screening test for cognitive deficits in ALS (the Edinburgh Cognitive and Behavioural ALS Screen), which will be described in more detail later.

When we compare the profile of language dysfunction described in this chapter with that of the two aphasic variants of FTD (PNFA and SD), it becomes clear that they demonstrate only partial overlap. The mute or almost mute ALS patients are different from those with PNFA, who often struggle for words but make every possible effort to produce them. The prominent impairment of verb and action processing in ALS shows the opposite pattern of predominant noun and object deficit in SD [55], although PNFA patients may show verb-predominant deficits. Thus, we believe that the language characteristics of FTD-ALS are distinguishable from those of the aphasic subtypes of FTD [1, 50], but further comparative investigation is warranted.

Social cognition in FTD-ALS

In the last five years neuropsychologists have directed their attention toward the investigation of changes in social cognition in ALS, given that this is a primary feature of FTD, with a particular focus on theory of mind and emotional processing. Theory of mind tests involve the ability to infer mental states in others. ALS patients have been shown to be impaired in the interpretation of social scenarios in stories and humorous cartoons, and in the understanding of faux pas through written stories [44]. A selective deficit in processing specifically social cartoon scenes was demonstrated by Cavallo *et al.* [56], in which ALS patients had particular difficulties in inferring a social intention compared with a private or “non-social” intention. A private intention involves a goal that is only relevant to one person (e.g., the person wants to read a book), compared with a social goal (e.g., the person wants another person to move their bag so they can sit down). A deficit has also been revealed on a simple theory of mind test in which the participant must infer the thoughts of another (depicted by a cartoon face) by the direction of eye gaze [42]. Here the participant must first choose their own favorite object from a choice of four objects; a central face then appears on the screen which is looking and smiling at one of the objects and the participant must choose which object the face likes best. ALS patients tend to repeatedly choose their own favorite object, indicating a difficulty in inhibiting their own preference, rather than the normative response of using a simple social cue of eye gaze to understand the perspective of another person.

ALS patients also show difficulties in processing emotions. Impairments have been revealed in the recognition of facial emotional expressions, and judgments of approachability on the basis of facial expressions [42, 57]. Furthermore, deficits have been found using the

Reading the Mind in the Eyes Test and also in judgments of emotional prosody [44]. Lulé *et al.* demonstrated that ALS patients tend to show a more positive valence towards emotive social situations and overall a more balanced state of arousal than controls, rating calm pictures as more exciting and vice versa [58], while Papps *et al.* revealed that ALS patients do not show the enhanced recognition of emotional words as found in healthy controls [59].

Behavior change in FTD-ALS

In their influential paper, Lomen-Hoerth *et al.* demonstrated that new-onset behavior change similar to that found in bvFTD was prevalent in ALS [60]. As measured using the Neuropsychiatric Inventory, apathy, disinhibition, and poor social monitoring were reported both in cases with letter fluency deficits and in others who had no evidence of cognitive change. In a detailed interview-based assessment of behavior change, self-centeredness/selfishness was described as the most prominent symptom followed by apathy, aggression, loss of insight, and social disinhibition. Apathy appears to be a particularly common behavioral feature of ALS and has typically been measured using the Frontal Systems Behavior Scale (FrSBe) [42, 61], although this assessment method has limitations and may exaggerate impairment due to physical disability. However, evidence for prevalent apathy in ALS has also been shown using the Cambridge Behaviour Inventory in which this symptom was reported in 41% of patients [62]. An ALS-specific behavior questionnaire has been designed which detected a lower prevalence of behavior change than the FrSBe although behavior change was still evident [63].

Psychiatric symptoms in FTD-ALS

As discussed earlier in this chapter, much of our current understanding of the FTD-ALS spectrum brings us back to the historical insights of the neurologists and psychiatrists of the early twentieth century. This is particularly true for the psychiatric features of the disease. Many symptoms mentioned in the classical papers on ALS, such as personality change, irritability, or emotional lability, could now be reinterpreted as belonging to the spectrum of bvFTD. However, several early descriptions also explicitly mention psychotic symptoms, specifically hallucinations and delusions, and speak of schizophrenia associated with ALS (for review see [1, 15]). More recent papers, focusing on other aspects of the disease, such as language, mention complex delusions, such as the “phantom lodger syndrome” [4]. Such psychotic symptoms are relatively rare in the classical FTD [64], so they constitute yet another difference between FTD and FTD-ALS. Indeed, the appearance of delusions in FTD patients is associated with a significantly higher risk of subsequent development of ALS [5].

The question of psychotic symptoms in FTD-ALS acquired a new dimension with the finding that delusions and hallucinations were particularly frequent among the patients with the *C9orf72* mutation [3]. But why have only some of the research groups found such an association and others not? This question was intensely debated at the Biennial Meeting of the World Federation of Neurology Research Group on Aphasia, Dementia and Cognitive Disorders (WFN RGADCD) in Hyderabad in December 2012. One option is that the patient cohorts examined at different research centers are indeed different. The other, suggested by one author of this chapter (THB), is that the difference lies in the assessment of patients. As mentioned before, most patients with FTD-ALS show a characteristic temporal pattern of the disease, starting with psychiatric symptoms and then

followed, months or years later, by cognitive and finally amyotrophic symptoms. So in many if not in most cases the psychotic symptoms are not present any more at the time the diagnosis of ALS is made. Patients and families would not likely recognize a connection between two features which appear as dissimilar as paranoia and muscle weakness, so the history of psychotic symptoms goes unnoticed. The only way to determine real prevalence of psychosis is a systematic enquiry. For this reason, our new screening instrument, which will be presented in detail below, contains, apart from the questions exploring the classical symptoms of bvFTD, also specific inquiry about a history of psychotic symptoms.

Assessing cognitive and behavior dysfunction in FTD-ALS

Despite the increased awareness of cognitive change as integral to the disease [24], the cognitive status of the majority of ALS patients attending clinics remains unknown [2, 54]. This reflects the orientation of many ALS neurologists (not recognizing the frequency of these symptoms) and the lack of expert clinical neuropsychology services associated with ALS or neuromuscular clinics; in addition, there has been a dearth of suitable screening tools for clinical use. Furthermore, the diversity of physical disability in ALS necessitates the use of specifically developed measures as well as expertise. Standard tests may not be suitable and may exaggerate performance deficits due to physical limitations.

Two cognitive screening examinations have been developed specifically for ALS. The first, the ALS Cognitive Behavior Screen (ALS-CBS) [65] is a very brief screen which assesses a single cognitive domain of executive functions. It contains eight short cognitive tests of executive

functions and a carer behavior questionnaire. It has been validated against a neuropsychological battery and successfully distinguishes those with cognitive impairment from those with no cognitive impairment with 85% sensitivity and 71% specificity. The second is the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), which is a multidomain, brief (15–20 minute) assessment for use within an MND clinic setting, for use also by non-neuropsychologists, such as physicians, speech pathologists, nurses, or other clinicians [53] (see [Figure 6.2](#)). It was designed to determine: (1) Which patients have cognitive and/or behavior impairment? (2) How severe is that impairment? And most importantly given the heterogeneity of presentation (3) What type of cognitive or behavioral impairment is present? The ECAS assesses functions which are specific to the cognitive profile of ALS (including executive and language functions, social cognition, and behavior). It also includes brief assessment of functions not specific to the cognitive profile of ALS (memory and visuospatial functions) but which are typically affected in other disorders common in older adults, namely Alzheimer's disease. Our recent work has demonstrated that of a cohort of 48 ALS patients (none with evident dementia), 29% were below cutoffs for abnormality on the ECAS total scores, with 35% showing abnormal language functions, and 23% executive and fluency deficits. The ECAS also includes a separate, brief carer behavior interview based on the recent criteria for diagnosis of bvFTD [9]. Forty percent of carers interviewed reported change in at least one behavioral domain, the most prevalent being apathy, which is in accord with previous findings. The cognitive and behavioral data from the ECAS are therefore consistent with prevalence rates demonstrated by studies using extensive neuropsychological batteries.


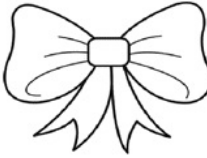
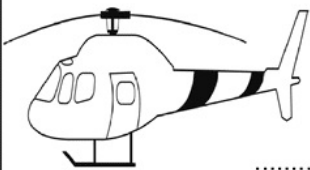
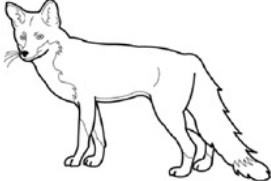



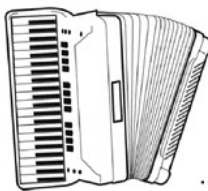
EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS English Version (2013)		
Date of testing: Age at leaving full-time education: Occupation: Handedness:	Name: Date of Birth: Hospital No. or Address:	
LANGUAGE - Naming		
➡ Ask: Say or write down the names of these pictures:		Score 0-8 <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	
 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	
 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	
 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	 <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block; vertical-align: middle;"></div>	
LANGUAGE - Comprehension		
➡ Ask: Point to the one which is:		Score 0-8 <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
1. Something you can fly in 3. An animal that climbs trees 5. A means of transport 7. Something with a sting	2. Something with webbed feet 4. Something used for chopping 6. Something with a sharp edge 8. Something with a diet of nuts and seeds	

Figure 6.2 Edinburgh Cognitive and Behavioural Screen [53].

Source: <https://www.era.lib.ed.ac.uk/bitstream/1842/6592/11/ECAS.pdf>

Why is it important to identify cognitive and/or behavioral symptoms in ALS? Cognitive change may impact on planning, attention, decision-making, and initiating ideas. Especially in the context of a condition as serious as ALS, clinicians must ensure that patients can fully understand the consequence of their decisions. Changes in behavior, personality, or social cognition may result in an egocentric perspective. After cognitive and/or behavior change is identified, carers, clinicians, and patients should be educated that these changes are part of the spectrum of symptoms of the disease. Hidden impairments may emerge as the patient faces new challenges in coping with their disability such as learning to use communication, feeding, or respiration aids. Difficulties with managing affairs or finances or end-of-life decisions may come to light. Furthermore, neurobehavioral symptoms have been associated with poor quality of life, increased depression and higher carer burden [66], while Lillo *et al.* [16] demonstrated that the strongest predictor of high caregiver burden was abnormal behaviors (such as disinhibition and impulsivity) which were over and above physical disability in ALS.

Brain imaging and cognition in FTD-ALS

A variety of imaging techniques have shown that cognitive symptoms in ALS are directly related to frontotemporal cortical and subcortical involvement [67–69]. Functional MRI (fMRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) have shown that verbal fluency deficits are associated with dysfunction of the dorsolateral prefrontal cortex and anterior cingulate gyrus [37, 67, 70]. Impairments in attention and inhibition have also recently been investigated using fMRI, with a profile of abnormal

activation in the medial prefrontal cortex, anterior cingulate gyrus, and temporal cortex [71]. Correlations between impairments in verbal fluency and naming and reduced flumazenil PET binding in the inferior frontal gyrus have also been reported, indicating a focal reduction in GABA receptors [72].

Studies on structural abnormalities have recently focused on white matter changes. One of the earlier studies using automated volumetric MRI analysis with patients with verbal fluency deficits showed a pattern of frontotemporal white matter change [31]. Further correlations with white matter tract abnormalities have been revealed using diffusion tensor MRI in which verbal fluency impairments have been correlated with a reduction in fractional anisotropy in the cingulum bundle [73] and inferior frontal gyrus white matter and corpus callosum, the latter being a key feature consistently across studies [41] (see Figure 6.3).

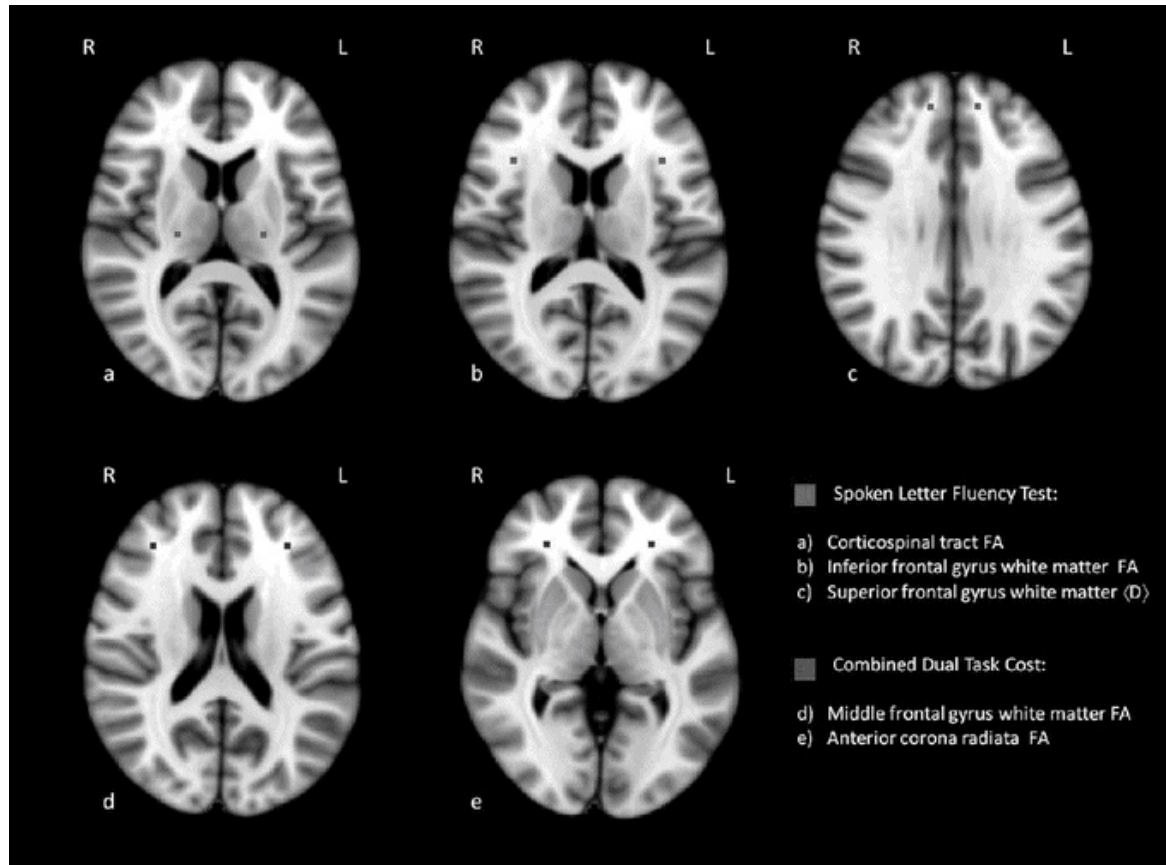


Figure 6.3 Cognitive performance correlates with white matter tract abnormalities using diffusion tensor MRI. Correlations between verbal fluency index (*Vfi*) and dual-task performance with fractional anisotropy (FA) and diffusivity, $\langle D \rangle$, diffusion tensor imaging measures in prefrontal and motor system tracts in ALS [41].

Dual-task impairments appear more strongly correlated with dorsolateral prefrontal dysfunction while letter fluency is more dependent on inferolateral prefrontal dysfunction [41]. Impairments in emotional processing have also been investigated with brain imaging and levels of arousal have been shown to correlate with activation in the anterior insula in ALS [58], while right hemispheric dysfunction was implicated in ALS during an emotional decision-making and recognition task [74]. Furthermore, impaired emotional empathy has been related to reduced gray matter density in the anterior cingulate cortex and right inferior frontal gyrus [75]. Greater apathy has been related to dysfunction of the anterior cingulum in ALS [76], while cortical atrophy was shown to be linked to both neuropsychiatric and cognitive changes in ALS [77].

Pathology of FTD-ALS

At the level of pathology, FTD and ALS show striking similarities. In the 1990s it was recognized that the brains of patients with ALS as well as those of a large number of tau-protein-negative cases of FTD (including most cases of SD and a large proportion of those with bvFTD) showed similar intracellular ubiquitin-positive inclusions. In 2006, the protein TDP-43 was identified in such inclusions [12]. Another relevant protein, FUS (fused in sarcoma protein), was described three years later [78]. From the molecular point of view, therefore, it is compelling to view FTD and ALS

as different manifestations of the same underlying processes. Their phenotypical variation can be explained by the different distribution of pathology (see [Chapter 13](#) for more detail).

Like most other neurodegenerative diseases, FTD and ALS begin usually with a relatively focal presentation, followed by a gradual but relentless progression. The nature of this progression is a topic of considerable interest. Within the classical motor presentation of ALS, large systematic clinicopathologic studies by Ravits and colleagues showed a focal initiation and a spread of the disease to functionally connected structures [79]. A similar method of investigation was recently undertaken in relation to the spread of TDP-43 in ALS [80] and in bvFTD [81]. A possible explanation for the functional link between the cognitive and the motor system as an axis of spread of pathology has been offered by Bak and Chandran [50], who propose to consider FTD-ALS as one of the focal presentations of ALS, alongside the bulbar and the limb-onset forms.

Genetics of FTD-ALS

Although clinical manifestations of a disease can be studied without any connection to the underlying pathology, the knowledge of pathologic changes often guides a physician to focus on specific clinical features and less so on others. It is conceivable, therefore, that much of the skepticism towards cognitive aspects of ALS stemmed from the fact that the first major genetic mutation found in this disease, *SOD1*, is associated with relatively well-preserved cognition [19]. For many years, *SOD1*-based models dominated ALS research. Thus, if the *SOD1* phenotype was considered to be the classical manifestation of the disease, cognitive and behavioral changes must have looked like a rare and potentially irrelevant confound.

The discovery of the *C9orf72* repeat expansion [13, 14] had exactly the opposite effect (see [Chapter 14](#) for more detail). The fact that this mutation, much more common than *SOD1*, could be associated with FTD as well as ALS directed the attention of the research community to a possible overlap between both diseases. Research centers all over the world set out to examine whether patients with this mutation show any characteristic features which would distinguish them from those without the mutation. One of the most prominent was the already mentioned high prevalence of psychosis in *C9orf72* patients [3]. However, it is important to remember that *C9orf72* does not explain all familial cases of overlap between FTD, ALS, and neuropsychiatric disorders [82].

While the *C9orf72* repeat expansion accounts for the largest percentage of FTD-ALS cases, other genes have also been implicated. A recent study describes a case of progressive aphasia associated with a mutation in the *OPTN* gene [83]. In contrast to the *C9orf72* gene, *OPTN* gene seems to be more frequent in Japan than in Europe and the exact cognitive profile of patients with *OPTN* mutation is still to be determined. The differential distribution of the two genes raises, however, the question of to what extent the clinical phenotypes, including cognitive and behavioral features, might be influenced by the specific genetic background of the population in question: an issue to be addressed by future research.

Conclusions

The fields of MND and FTD are changing rapidly. Advances in molecular biology and genetics are illuminating the pathologic processes. The discovery of the *C9orf72* gene mutation is likely to be followed by the identification of new genes and characteristic phenotypes associated with

them. Of course, we hope that these discoveries are translated into new treatments as soon as possible.

And yet, underlying these breathtaking advances, there is a long tradition of related insights and observations. As pointed out in the introduction to this chapter, much of the current knowledge about the frequency, pattern, and natural history of cognitive and behavioral symptoms in ALS, including the idea of the ALS/FTD overlap, was observed before 1950. What has changed most dramatically are not the insights themselves, but the way in which they influence everyday clinical practice. The overlap between ALS and FTD is by now widely recognized by clinicians; cognitive assessment is becoming an integral part of the clinical evaluation of patients with MND, and cognitive status is likely to become an important variable in the evaluation of future pharmacologic trials. Thus, the relationship between ALS and FTD (and, in broader terms, between motor and cognitive functions in general [84]) has moved from a rare curiosity reported at the periphery of scientific developments into the very heart of current research and clinical practice.

References

1. Bak TH. Motor neuron disease and frontotemporal dementia: one, two, or three diseases? *Annals of Indian Academy of Neurology* 2010;**13**(Suppl 2):S81.
2. Bak TH. The importance of looking in dark places. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2013;**14**(1):1–2.
3. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, *et al.* Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations. *Brain* 2012;**135**(3):693–708.

-
4. Bak TH, O'Donovan DG, Xuereb JH, Boniface S, Hodges JR. Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease – dementia – aphasia syndrome. *Brain* 2001;**124**(1):103–20.
-
5. Lillo P, Garcin B, Hornberger M, Bak TH, Hodges JR. Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis. *Archives of Neurology* 2010;**67**(7):826–30.
-
6. Mioshi E, Caga J, Lillo P, Hsieh S, Ramsey E, Devenney E, *et al.* Neuropsychiatric changes precede classic motor symptoms in ALS and do not affect survival. *Neurology* 2014;**82**(2):149–55. doi: 10.1212/WNL.0000000000000023.
-
7. Hudson AJ. Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: a review. *Brain* 1981;**104**(2):217–47.
-
8. Neary D, Snowden J, Mann D, Northen B, Goulding P, Macdermott N. Frontal lobe dementia and motor neuron disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 1990;**53**(1):23–32.
-
9. Rascofsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;**134**(9):2456–77.
-
10. Gorno-Tempini M, Hillis A, Weintraub S, Kertesz A, Mendez M, Cappa S, *et al.* Classification of primary progressive aphasia and its variants. *Neurology* 2011;**76**(11):1006–14.
-
11. Bak TH, Hodges JR. Cognition, language and behaviour in motor neurone disease: evidence of frontotemporal dysfunction. *Dementia and Geriatric Cognitive Disorders* 1999;**10**(Suppl 1):29–32.

12. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, *et al.* Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;**314**(5796):130–3.

13. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;**72**(2):245–56.

14. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;**72**(2):257–68.

15. Bak TH, Hodges JR. Motor neurone disease, dementia and aphasia: coincidence, co-occurrence or continuum? *Journal of Neurology* 2001;**248**(4):260–70.

16. Lillo P, Savage S, Mioshi E, Kiernan MC, Hodges JR. Amyotrophic lateral sclerosis and frontotemporal dementia: a behavioural and cognitive continuum. *Amyotrophic Lateral Sclerosis* 2012;**13**(1):102–9.

17. Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, *et al.* Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis* 2009;**10**(3):131–46.

18. Taylor LJ, Brown RG, Tsermentseli S, Al-Chalabi A, Shaw CE, Ellis CM, *et al.* Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis? *Journal of Neurology, Neurosurgery, and Psychiatry* 2013;**84**(5):494–8.

19. Goldstein L. SOD1 and cognitive dysfunction in familial amyotrophic lateral sclerosis. *Journal of Neurology* 2009;**256**(2):234–41.

-
- 20.** Canu E, Agosta F, Galantucci S, Chiò A, Riva N, Silani V, *et al.* Extramotor damage is associated with cognition in primary lateral sclerosis patients. *PloS One* 2013;**8**(12):e82017.
-
- 21.** Silani V, Poletti B, Zago S. Frontotemporal syndromes of primary lateral sclerosis. In Strong MJ, ed. *Amyotrophic Lateral Sclerosis and the Frontotemporal Dementias* Oxford, UK: Oxford University Press. 2012; 171–86.
-
- 22.** Raaphorst J, de Visser M, van Tol M-J, Linssen WH, van der Kooi AJ, de Haan RJ, *et al.* Cognitive dysfunction in lower motor neuron disease: executive and memory deficits in progressive muscular atrophy. *Journal of Neurology, Neurosurgery, and Psychiatry* 2011;**82**(2):170–5.
-
- 23.** Wicks P, Abrahams S, Leigh P, Williams T, Goldstein L. Absence of cognitive, behavioral, or emotional dysfunction in progressive muscular atrophy. *Neurology* 2006;**67**(9):1718–19.
-
- 24.** Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. *Lancet Neurology* 2013;**12**(4):368–80.
-
- 25.** Kew J, Leigh N. Dementia with motor neurone disease. *Bailliere's Clinical Neurology* 1992;**1**(3):611–26.
-
- 26.** Barson F, Kinsella G, Ong B, Mathers S. A neuropsychological investigation of dementia in motor neurone disease (MND). *Journal of the Neurological Sciences* 2000;**180**(1):107–13.
-
- 27.** Ringholz G, Appel S, Bradshaw M, Cooke N, Mosnik D, Schulz P. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005;**65**(4):586–90.
-
- 28.** Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, *et al.* The

syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *Journal of Neurology, Neurosurgery, and Psychiatry* 2012;**83**(1):102–8.

29. Abrahams S, Leigh P, Harvey A, Vythelingum G, Grise D, Goldstein L. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). *Neuropsychologia* 2000;**38**(6):734–47.

30. Raaphorst J, De Visser M, Linssen WH, De Haan RJ, Schmand B. The cognitive profile of amyotrophic lateral sclerosis: a meta-analysis. *Amyotrophic Lateral Sclerosis* 2010;**11**(1–2):27–37.

31. Abrahams S, Leigh P, Goldstein L. Cognitive change in ALS: a prospective study. *Neurology* 2005;**64**(7):1222–6.

32. Elamin M, Bede P, Byrne S, Jordan N, Gallagher L, Wynne B, *et al.* Cognitive changes predict functional decline in ALS: a population-based longitudinal study. *Neurology* 2013;**80**(17):1590–7.

33. Olney R, Murphy J, Forsheew D, Garwood E, Miller B, Langmore S, *et al.* The effects of executive and behavioral dysfunction on the course of ALS. *Neurology* 2005;**65**(11):1774–7.

34. Elamin M, Phukan J, Bede P, Jordan N, Byrne S, Pender N, *et al.* Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. *Neurology* 2011;**76**(14):1263–9.

35. Abrahams S, Goldstein L, Al-Chalabi A, Pickering A, Morris R, Passingham R, *et al.* Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 1997;**62**(5):464–72.

36. Massman P, Sims J, Cooke N, Haverkamp L, Appel V, Appel S. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 1996;**61**(5):450–5.

-
- 37.** Abrahams S, Goldstein L, Kew J, Brooks D, Lloyd C, Frith C, *et al.* Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. *Brain* 1996;**119**(6):2105–20.
-
- 38.** Donaghy C, Pinnock R, Abrahams S, Cardwell C, Hardiman O, Patterson V, *et al.* Ocular fixation instabilities in motor neurone disease. *Journal of Neurology* 2009;**256**(3):420–6.
-
- 39.** Witgert M, Salamone A, Strutt A, Jawaid A, Massman P, Bradshaw M, *et al.* Frontal-lobe mediated behavioral dysfunction in amyotrophic lateral sclerosis. *European Journal of Neurology* 2010;**17**(1):103–10.
-
- 40.** Libon DJ, McMillan C, Avants B, Boller A, Morgan B, Burkholder L, *et al.* Deficits in concept formation in amyotrophic lateral sclerosis. *Neuropsychology* 2012;**26**(4):422–9.
-
- 41.** Pettit LD, Bastin ME, Smith C, Bak TH, Gillingwater TH, Abrahams S. Executive deficits, not processing speed relates to abnormalities in distinct prefrontal tracts in amyotrophic lateral sclerosis. *Brain* 2013;**136**(11):3290–304.
-
- 42.** Girardi A, MacPherson SE, Abrahams S. Deficits in emotional and social cognition in amyotrophic lateral sclerosis. *Neuropsychology* 2011;**25**(1):53–65.
-
- 43.** Štukovnik V, Zidar J, Podnar S, Repovš G. Amyotrophic lateral sclerosis patients show executive impairments on standard neuropsychological measures and an ecologically valid motor-free test of executive functions. *Journal of Clinical and Experimental Neuropsychology* 2010;**32**(10):1095–109.
-
- 44.** Meier SL, Charleston AJ, Tippet L. Cognitive and behavioural deficits associated with the orbitomedial prefrontal cortex in amyotrophic lateral sclerosis. *Brain* 2010;**133**(11):3444–57.
-
- 45.** Caselli RJ, Windebank AJ, Petersen RC, Komori T, Parisi JE, Okazaki H, *et al.* Rapidly progressive aphasic dementia and motor neuron disease. *Annals of*

Neurology 1993;**33**(2):200–7.

46. Bak T, Hodges J. Noun-verb dissociation in three patients with motor neuron disease and aphasia. *Brain and Language* 1997;**60**(1):38–41.

47. Bak TH, Hodges JR. The effects of motor neurone disease on language: further evidence. *Brain and Language* 2004;**89**(2):354–61.

48. Hillis AE, Heidler-Gary J, Newhart M, Chang S, Ken L, Bak TH. Naming and comprehension in primary progressive aphasia: the influence of grammatical word class. *Aphasiology* 2006;**20**(02–04):246–56.

49. Grossman M, Anderson C, Khan A, Avants B, Elman L, McCluskey L. Impaired action knowledge in amyotrophic lateral sclerosis. *Neurology* 2008;**71**(18):1396–401.

50. Bak TH, Chandran S. What wires together dies together: verbs, actions and neurodegeneration in motor neuron disease. *Cortex* 2012;**48**(7):936–44.

51. Bak TH. The neuroscience of action semantics in neurodegenerative brain diseases. *Current Opinion in Neurology* 2013;**26**(6):671–7.

52. Ichikawa H, Hieda S, Ohno H, Ohnaka Y, Shimizu Y, Nakajima M, *et al.* Kana versus kanji in amyotrophic lateral sclerosis: a clinicoradiological study of writing errors. *European Neurology* 2010;**64**(3):148–55.

53. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2014;**15**(1–2):9–14.

54. Abrahams S. Executive dysfunction in ALS is not the whole story. *Journal of Neurology, Neurosurgery, and Psychiatry* 2013;**84**(5):474–5.

55. Bak TH, Hodges JR. Kissing and dancing – a test to distinguish the lexical and conceptual contributions to noun/verb and action/object dissociation.

Preliminary results in patients with frontotemporal dementia. *Journal of Neurolinguistics* 2003;**16**(2):169–81.

56. Cavallo M, Adenzato M, MacPherson SE, Karwig G, Enrici I, Abrahams S. Evidence of social understanding impairment in patients with amyotrophic lateral sclerosis. *PloS One* 2011;**6**(10):e25948.

57. Schmolck H, Mosnik D, Schulz P. Rating the approachability of faces in ALS. *Neurology* 2007;**69**(24):2232–5.

58. Lulé D, Diekmann V, Kassubek J, Kurt A, Birbaumer N, Ludolph AC, *et al.* Cortical plasticity in amyotrophic lateral sclerosis: motor imagery and function. *Neurorehabilitation and Neural Repair* 2007;**21**(6):518–26.

59. Papps B, Abrahams S, Wicks P, Leigh P, Goldstein L. Changes in memory for emotional material in amyotrophic lateral sclerosis (ALS). *Neuropsychologia* 2005;**43**(8):1107–14.

60. Lomen-Hoerth C, Murphy J, Langmore S, Kramer J, Olney R, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003;**60**(7):1094–7.

61. Grossman AB, Woolley-Levine S, Bradley WG, Miller RG. Detecting neurobehavioral changes in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis* 2007;**8**(1):56–61.

62. Lillo P, Mioshi E, Zoing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyotrophic lateral sclerosis? *Amyotrophic Lateral Sclerosis* 2011;**12**(1):45–51.

63. Raaphorst J, Beeldman E, Schmand B, Berkhout J, Linssen WH, van den Berg LH, *et al.* The ALS-FTD-Q: a new screening tool for behavioral disturbances in ALS. *Neurology* 2012;**79**(13):1377–83.

64. Bak TH, Crawford LM, Berrios G, Hodges JR. Behavioural symptoms in

progressive supranuclear palsy and frontotemporal dementia. *Journal of Neurology, Neurosurgery, and Psychiatry* 2010;**81**(9):1057–9.

65. Woolley SC, York MK, Moore DH, Strutt AM, Murphy J, Schulz PE, *et al.* Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive Behavioral Screen (ALS-CBS™). *Amyotrophic Lateral Sclerosis* 2010;**11**(3):303–11.

66. Chiò A, Vignola A, Mastro E, Giudici AD, Iazzolino B, Calvo A, *et al.* Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life. *European Journal of Neurology* 2010;**17**(10):1298–303.

67. Abrahams S, Goldstein L, Simmons A, Brammer M, Williams S, Giampietro V, *et al.* Word retrieval in amyotrophic lateral sclerosis: a functional magnetic resonance imaging study. *Brain* 2004;**127**(7):1507–17.

68. Bastin ME, Pettit LD, Bak TH, Gillingwater TH, Smith C, Abrahams S. Quantitative tractography and tract shape modeling in amyotrophic lateral sclerosis. *Journal of Magnetic Resonance Imaging* 2013;**38**(5):1140–5.

69. Bede P, Elamin M, Byrne S, McLaughlin RL, Kenna K, Vajda A, *et al.* Basal ganglia involvement in amyotrophic lateral sclerosis. *Neurology* 2013;**81**(24):2107–15.

70. Kew J, Goldstein L, Leigh P, Abrahams S, Cosgrave N, Passingham R, *et al.* The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis. A neuropsychological and positron emission tomography study. *Brain* 1993;**116**(6):1399–423.

71. Goldstein L, Newsom-Davis I, Bryant V, Brammer M, Leigh P, Simmons A. Altered patterns of cortical activation in ALS patients during attention and cognitive response inhibition tasks. *Journal of Neurology* 2011;**258**(12):2186–98.

72. Wicks P, Turner MR, Abrahams S, Hammers A, Brooks DJ, Leigh PN, *et*

al. Neuronal loss associated with cognitive performance in amyotrophic lateral sclerosis: an (11C)-flumazenil PET study. *Amyotrophic Lateral Sclerosis* 2008;**9**(1):43–9.

73. Sarro L, Agosta F, Canu E, Riva N, Prella A, Copetti M, *et al.* Cognitive functions and white matter tract damage in amyotrophic lateral sclerosis: a diffusion tensor tractography study. *American Journal of Neuroradiology* 2011;**32**(10):1866–72.

74. Palmieri A, Naccarato M, Abrahams S, Bonato M, D'Ascenzo C, Balestreri S, *et al.* Right hemisphere dysfunction and emotional processing in ALS: an fMRI study. *Journal of Neurology* 2010;**257**(12):1970–8.

75. Cerami C, Dodich A, Canessa N, Crespi C, Iannaccone S, Corbo M, *et al.* Emotional empathy in amyotrophic lateral sclerosis: a behavioural and voxel-based morphometry study. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2014;**15**(1–2):21–9.

76. Woolley SC, Zhang Y, Schuff N, Weiner MW, Katz JS. Neuroanatomical correlates of apathy in ALS using 4 Tesla diffusion tensor MRI. *Amyotrophic Lateral Sclerosis* 2011;**12**(1):52–8.

77. Mioshi E, Lillo P, Yew B, Hsieh S, Savage S, Hodges JR, *et al.* Cortical atrophy in ALS is critically associated with neuropsychiatric and cognitive changes. *Neurology* 2013;**80**(12):1117–23.

78. Munoz DG, Neumann M, Kusaka H, Yokota O, Ishihara K, Terada S, *et al.* FUS pathology in basophilic inclusion body disease. *Acta Neuropathologica* 2009;**118**(5):617–27.

79. Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology* 2009;**73**(10):805–11.

80. Brettschneider J, Del Tredici K, Toledo JB, Robinson JL, Irwin DJ,

Grossman M, *et al.* Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. *Annals of neurology* 2013;**74**(1):20–38.

81. Brettschneider J, Del Tredici K, Irwin DJ, Grossman M, Robinson JL, Toledo JB, *et al.* Sequential distribution of pTDP-43 pathology in behavioral variant frontotemporal dementia (bvFTD). *Acta Neuropathologica* 2014;**127**(3):423–39.

82. Byrne S, Heverin M, Elamin M, Bede P, Lynch C, Kenna K, *et al.* Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: a population-based case–control cohort study of familial and sporadic amyotrophic lateral sclerosis. *Annals of Neurology* 2013;**74**(5):699–708.

83. Czell D, Andersen PM, Neuwirth C, Morita M, Weber M. Progressive aphasia as the presenting symptom in a patient with amyotrophic lateral sclerosis with a novel mutation in the *OPTN* gene. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2013;**14**(2):138–40.

84. Bak TH. Movement disorders: why movement and cognition belong together. *Nature Reviews Neurology* 2010;**7**(1):10–12.

Chapter 7

Progressive supranuclear palsy and corticobasal degeneration in the FTD spectrum



Barbara Borroni and Antonella Alberici

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

In 1892, Arnold Pick described progressively aphasic patients with behavioral disturbances and frontal lobar atrophy [[1](#)]. Subsequent neuropathologic studies emphasized the evidence of focal frontal atrophy along with the presence of round silver-staining inclusions (Pick bodies) and ballooned neurons (Pick cells). Pick's disease was subsequently used to classify patients with those findings at autopsy, which turned out to be observed in only some cases with clinical frontotemporal dementia (FTD). The paradox of FTD without Pick bodies gave rise to one of the first controversies about the nosology of this disease, in which the gross pattern

of lobar atrophy was the main characteristic, but with a wide variety of clinical and pathologic features.

Almost 40 years later, the recognition of an extrapyramidal involvement in FTD patients further complicated the classification of these diseases. Indeed, after the initial description of Pick's disease, von Braünmuhl *et al.* reported cases with atrophy extending from frontal lobe to basal ganglia, in particular the caudate nucleus [2]. A few years later, in 1944, Akelaitis described a patient with an early parkinsonian syndrome associated with confusion and apathy, who showed a progressive deterioration of motor status, behaviour, and language, dying demented approximately five years after disease onset [3]. At pathologic examination, atrophy was detected not exclusively in the frontal cortex, but also in the subcortical gray regions, with a severe involvement of the caudate nucleus. For some years, the “Akelaitis variant” was applied to patients who were recognized as having prominent extrapyramidal symptoms associated with FTD. The occurrence of parkinsonism along with an involvement of basal ganglia and nigrostriatal degeneration in Pick's disease gave rise to a scientific debate, but at the same time promoted the concept of inclusion of different clinical and pathologic entities within the FTD spectrum.

Twenty years after the Akelaitis report, Steele and colleagues provided the description of a clinical syndrome defined by supranuclear ophthalmoplegia, mainly affecting vertical gaze, pseudobulbar palsy, dysarthria, dystonic axial rigidity along with variable cerebellar and pyramidal symptoms, mildly progressive toward dementia, and involving the brainstem [4]. The characterization of progressive supranuclear palsy (PSP) was soon followed by the report of another extrapyramidal condition affecting three patients who had been evaluated by Rebeiz and colleagues at the Massachusetts General Hospital [5]. The “*strange*” disorder that “*defied all attempts at exact diagnosis and effective treatment*” was

named as corticodentatonigral degeneration with neuronal achromasia, later known as corticobasal degeneration syndrome (CBDS) [6]. The first reports of CBDS patients outlined the combination of a severe motor impairment with cerebral cortical deficits. In particular, the initial asymmetric awkwardness and involuntary movements, variably involving rigidity, tremor, and dystonia, also included language deficits, apraxia, alien limb, and cortical sensory loss. Autopsy examination revealed strikingly asymmetric frontal and parietal atrophy with involvement of white matter, as well as basal ganglia, including the substantia nigra and the subthalamic nucleus. In the Rebeiz *et al.* paper [7], PSP was suggested to share some clinical features with CBDS cases: the similar age and the slowly progressive course of a movement disorder with cognitive impairment. However, CBDS exhibited neuropathology primarily in the cerebral frontal and parietal cortices, while PSP showed major brainstem involvement with a lesser degree of frontal cortical involvement.

Some early investigators included extrapyramidal cases within the spectrum of FTD. Constantinidis and colleagues proposed that the “variant B” with ballooned neurons had the most frequent extrapyramidal symptoms [8]. In a comparative clinical and pathologic investigation between cases with classic Pick's disease and a “generalized” variant, which included cases with cortical as well as subcortical atrophy, Munoz-Garcia and Ludwin distinguished the two series on the basis of inclusion type, and age of onset, being younger in the “generalized” variant [9]. Although Neary *et al.* [10] and the Lund and Manchester Groups [11] did not consider extrapyramidal variants in their original criteria, the increasing evidence that PSP, CBDS, and extrapyramidal syndromes shared clinical and pathologic overlap with FTD suggested a more integrated approach, eventually prompting their inclusion in consensus papers [10, 12].

An extensive clinicopathologic study of a prospective, clinic-based large cohort of patients with autopsy examination demonstrated how the first most common clinical presentation, in particular the behavioral variant of FTD (bvFTD), could be followed during disease progression by other syndromes, variably represented by primary progressive aphasias (PPAs), motor neuron disease (MND), or CBDS [13]. In analogy to bvFTD, also PPAs, CBDS, or PSP could evolve towards different clinical conditions [13] (see [Chapter 2](#) for more detail). Indeed, the clinical features poorly predicted the histopathologic characteristics, supporting the view of a wide heterogeneity in the FTD spectrum.

The great advances in genetic investigations further contributed in the identification of the common determinants among PSP, CBDS, and extrapyramidal components in FTD [14]. Concomitantly, the growing knowledge of neuropathologic hallmarks has allowed the scientific community to highlight the specific features of these disorders, and to refer to PSP and corticobasal degeneration (CBD) as distinctive neuropathologic entities within the frontotemporal lobar degeneration (FTLD) spectrum.

Neuropathology and genetics of PSP and CBD

The original description by Steele *et al.* reported as the main pathologic features of PSP to be the presence of cell loss, gliosis, neurofibrillary tangles, granulovacuolar degeneration, and demyelination in different regions of basal ganglia, brainstem, and cerebellum [4]. The most severely affected regions were the globus pallidus, subthalamic nucleus, red nucleus, substantia nigra, superior colliculi, nuclei cuneiformis and subcuneiformis, periaqueductal gray matter, pontine tegmentum, and dentate nucleus, with a

general preservation of cerebral cortex. On the contrary, the relevant findings by Rebeiz *et al.* in the cases of CBD included convolutional atrophy of frontal and parietal regions, with a pronounced asymmetric involvement, and consistently affecting some subcortical nuclei, including the substantia nigra, the subthalamic nucleus, and the dentate and roof nuclei of the cerebellum [7]. In CBD, astrocytic gliosis accompanied the loss of neurons; some astrocytes exhibited a peculiar pallor of staining named achromasia.

At present, the distinctive neuropathologic features of PSP include globose neurofibrillary tangles, oligodendroglial coiled bodies, tuft-shaped astrocytes, and thread-like processes, while CBD includes pre-tangle lesions, astrocytic plaques, and ballooned neurons [15–17]. The structural elements of these different morphologic entities are known to be determined by deposits of insoluble and hyperphosphorylated tau protein, which is invariably detected in PSP as well as CBD. Because of the sharing of common deposition of tau in PSP and CBD, the two pathologies are grouped within FTD-tau or tauopathies [14].

Tau is a protein specific to human brain tissue, present in neurons as well as glia, and known to promoting the assembly, spatial organization, and disassembly of microtubules in axons of neurons [18]. It is composed of 352–441 amino acids, and contains a characteristic tandem repeat region in its carboxyl-terminal half [19]. Tau is developmentally regulated, with six isoforms that differ by a 29–58-amino acid insert at the N-terminus, and a 31-amino acid repeat located in the C-terminus. The tandem repeat region constitutes the microtubule-binding domains of tau. The inclusion of the C-terminus repeat generates isoforms with 4 tandem repeats (4R), the others having 3 tandem repeats (3R). In Alzheimer's disease (AD), tau constitutes the core of paired helical filaments, the major components of neurofibrillary tangle. In tauopathies, 3R tau predominates in Pick's disease, whereas 4R

tau is most prevalent in PSP and CBD. As one pathogenic mechanism, the 4R isoforms have a lower ability to promote microtubule assembly than 3R tau, thus directly affecting tau/tubulin interaction [20]. Although PSP and CBD pathologies are commonly sustained by an abnormal deposition of tau, the different anatomical distribution of 4R deposits in PSP and CBD is thought to relate to the wide and overlapping spectrum of clinical presentations. Interestingly, a subtle alternative biochemical proteolytic process of tau, differently affecting PSP and CBD, has been claimed as a possible mechanism to distinguish the two pathologies [21]. Genetic analyses further contributed to demonstrate the presence of common determinants in PSP and CBD, in particular the discovery of missense and 5' splice-site mutations in the *MAPT* gene causing genetic cases of PSP and more rarely CBD (see Alzheimer Disease & Frontotemporal Dementia Database <http://www.molgen.ua.ac.be/FTDmutations/> and Table 7.1). Moreover, the *MAPT* H1 haplotype is a common genetic risk factor for PSP and CBD [22, 23], with specific polymorphisms associated to the diseases [24, 25]. Also from a genome-wide association study, *MAPT* was confirmed as strictly influencing both pathologies [26].

Table 7.1 *MAPT* mutations leading to either PSP or CBD

Disease	<i>MAPT</i> mutation	Reference
CBD	<i>MAPT</i> Pro301Ser (g.123789C>T)	[76]
PSP	<i>MAPT</i> Arg5Leu (g.75756G>T)	[77]
	<i>MAPT</i> ΔN296 (g.123775_123777delATA)	[78–81]
	<i>MAPT</i> Gly303Val (g.123796G>T)	[82, 83]

Although PSP and CBD are usually sporadic, occasional reports of familial aggregation, some with an autosomal dominant pattern of inheritance, may provide clues relevant to understanding the pathogenesis of these diseases [[27](#), [28](#)].

Clinical phenotypes associated with PSP and CBD

PSP and CBD are considered rare neurodegenerative disorders [[29](#)], and for this reason for many years only anecdotal cases describing clinical features have been available. However, the knowledge about the clinical features associated with PSP and CBD neuropathologic entities is rapidly expanding, and in the last years new diagnostic criteria have been proposed to highlight distinctive hallmarks able to predict the neuropathology [[30](#), [31](#)].

PSP and CBD were originally defined as atypical extrapyramidal syndromes with spared cortical functions. The most recent literature contradicted this point and has demonstrated that cognitive disturbances, and deficits of executive functions in particular, are more common than previously thought. These aspects have supported the inclusion of these conditions in the FTLD spectrum, and have further complicated the diagnostic process [[13](#)].

Indeed, one of the most intriguing issues at present is to define the genotype–phenotype relationship, as mismatch between clinical features and neuropathologic characteristics exist.

Recent clinicopathologic studies have led to the appreciation of several clinical syndromes associated with the pathology of PSP and CBD with initial clinical presentations more consistent with PPA or FTD [[32](#)].

Conversely, clinical features resembling PSP or CBD may be the initial presentation of other neuropathologic diagnoses, such as FTD with tau or transactive response DNA-binding protein 43 (TDP-43) inclusions, AD, α -synucleinopathies, and spongiform encephalopathy [33–35].

The early clinical features of either PSP or CBD are often subtle and can be difficult to discern [36]. To increase diagnostic accuracy, a careful characterization of the different clinical syndromes associated with PSP and CBD pathology has been proposed.

PSP current criteria and clinical phenotypes. In PSP, early diagnosis is a challenge, with fewer than half of patients receiving an accurate diagnosis initially; as many as 20% of patients will have a different diagnosis at the time of death [37–39].

There are many proposed clinical criteria for PSP, compiled to identify PSP-tau pathology, but the majority of them have a similar characteristic: high specificity and low sensitivity [31]. The National Institute of Neurological Disorders and Stroke/Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria state that early falls due to postural instability and supranuclear gaze palsy or slowed vertical saccades are the most helpful defining clinical features [31]. Along with current diagnostic criteria, a more detailed description of clinical phenotypes associated with PSP-tau has been proposed, to increase diagnostic accuracy.

The classical and more common phenotype has been termed Richardson's syndrome (PSP-RS), after J. C. Richardson's original description along with J. Steele and J. Olszewski [4]. It is characterized by lurching gait and unexplained falls backwards without loss of consciousness. Patients usually present with axial rigidity, and retrocollis is a common form of dystonia. Ocular symptoms give the syndrome its name, as vertical supranuclear gaze palsy is the definitive diagnostic feature even though this commonly develops many years after disease onset. Slow

saccades and involuntary eyelid closure due to blepharospasm may be adjunctive features. In PSP-RS, cognitive and behavioral deficits are often observed, including impairment of executive functions, aphasia or apraxia of speech, or apathy. On exam, it is often possible to elicit the “applause sign,” an indicator of impaired motor control leading to perseveration (repeated clapping despite instruction to clap only once) due to frontal dysfunction. Apraxia, even if less common than in CBD cases, and deficits of visuospatial functions are frequently observed. Apathy is the most common behavioral abnormality. Most patients become dependent on others for care within three to four years of diagnosis and the common causes of death are aspiration pneumonia due to dysphagia, primary neurogenic respiratory failure, and complications due to hip fractures.

PSP-parkinsonism (PSP-P), the second most common clinical phenotype, is characterized by bradykinesia, rigidity, and sometimes tremor, which tends to be asymmetric and at least modestly responsive to levodopa therapy. Parkinsonism dominates the early clinical picture and a jerky postural tremor and even a 4–6 Hz rest tremor are common in PSP-P patients. Falls and cognitive impairment occur later in PSP-P than in PSP-RS. However, after six years from the onset, PSP-RS and PSP-P tend to overlap and to be indistinguishable.

Another variant, known as pure akinesia with gait freezing (PSP-PAGF), has hypophonia and micrographia along with gait disturbance and later gait freezing. Usually, neither tremor, rigidity, dementia, nor eye movement abnormality are observed during the first five years of the disease.

Progressive apraxia of speech typically evolves into progressive non-fluent aphasia (PNFA), and this PSP-PNFA variant may have no aspects of classic PSP, at least at presentation. The clinical presentation is consistent

with non-fluent spontaneous speech, hesitancy, phonemic errors, and agrammatism. Motor features of PSP may develop later.

The classic corticobasal syndrome (CBS) has also been described in association with PSP pathology, and is termed PSP-CBS.

CBD current criteria and clinical phenotypes. The relationship between CBD neuropathology and clinical phenotype is one of the most challenging issues in the neurodegenerative disease field, since there is such variable correspondence between autopsy findings and the clinical picture. Early literature on CBD suggested that it was a distinct clinic pathologic entity; however, over the last years there is a strong body of literature indicating considerable heterogeneity [40]. Hitherto, we currently referred to the classical clinical picture as CBS, and to the pathologic entity as CBD [41].

Previously suggested criteria for CBD [42–47] have outlined the clinical features now labeled CBS, reflecting an asymmetric movement disorder presentation combined with lateralized higher cortical features. The core features include basal ganglia dysfunction as reflected by a varying combination of stiffness, clumsiness, and dystonia, with lack of sustained levodopa response, and cortical dysfunction characterized by ideomotor apraxia, alien limb phenomenon, cortical sensory loss, visual or sensory hemineglect, myoclonus, and language deficits. However, recent observations have highlighted that cognitive impairment is a common presenting clinical feature [47].

Different neuropathologic series have demonstrated that a relatively small proportion of cases with a CBS presentation turn out to be CBD at autopsy [41, 48–50], suggesting that current criteria are not able to identify CBD with high accuracy. To address this problem, a recent consensus conference has developed a set of new research criteria [30]. On the bases of data derived from brain-bank cases and a critical literature review, five

phenotypes have been described as being most frequently associated with CBD pathology: classical CBS, PSP syndrome (PSPS, also called Richardson's syndrome), FTD, AD-like dementia, and PNFA [30].

In this view, in order to maximize the chance of diagnosing classic CBD without contamination from other pathologies, the new criteria included cases with insidious onset and gradual progression lasting more than one year in people with symptom onset occurring after the age of 50, presenting as classical CBS but including features resembling frontal behavioral-spatial syndromes and non-fluent/agrammatic variant of primary progressive aphasia. Possible CBD criteria allowed the inclusion of PSPS phenotype.

However, it has also become evident that a substantial number of cases presenting as CBS do not have CBD pathology at autopsy. Because of this, stringent exclusion criteria have been developed to exclude Lewy body disease (i.e., classic 4 Hz Parkinson's disease resting tremor, excellent and sustained levodopa response, or hallucinations), multiple system atrophy (i.e., dysautonomia or prominent cerebellar signs), amyotrophic lateral sclerosis (i.e., presence of both upper and lower motor neuron signs), non-tau pathology (i.e., granulin mutation or reduced plasma progranulin levels, TDP-43 mutations, FUS mutations), and AD (i.e., low cerebrospinal fluid [CSF] amyloid- β (A β) and high CSF tau levels or positive amyloid PET scan, even though this will exclude some cases of CBD with coexisting amyloid) [30].

The proposed criteria will obviously need prospective study and continued revision and the development of new biomarkers will likely be key to the identification of CBD patients during life.

Brain imaging in PSP and CBD

Conventional structural neuroimaging has been proposed as an adjunctive tool to corroborate diagnosis in PSP and in CBS/CBD. However, the main limitation of many of these studies is the lack of autopsy confirmation.

In PSP, it is indeed widely established that the classical finding is represented by the “penguin/hummingbird sign,” given by the atrophy of the rostral midbrain tegmentum, the pontine base, and the cerebellum [51]. This finding appears highly specific for PSP, when disease is overt, present in 75% of cases, even if not pathognomonic for the disorder [51]. The areas of midbrain, pons, and cerebellar peduncles have also been used for quantitative analyses of regional atrophy, showing high sensitivity and specificity [52–55]. More recently, an automated computer classification based on MRI pattern analysis in parkinsonian syndromes was carried out, reporting 91% accuracy, 88% specificity, and 93% sensitivity in diagnosing PSP [56].

Advanced structural neuroimaging techniques, such as voxel-based morphometry and diffusion tensor imaging, have been used at group level and have helped in elucidating the clinical aspects associated with PSP. PSP is indeed characterized by involvement of brainstem and basal ganglia regions, but a reduced gray matter density in fronto-insular cortices has been reported, explaining the overlap with FTD symptoms in these patients [57–59]. Interestingly, these quantitative approaches can support a better definition of the anatomical correlates of the different entities in the clinical spectrum of PSP. PSP-RS is defined by more severe involvement of infratentorial white matter tracts and thalamic radiations, which are relatively spared in PSP-P [60, 61].

One of the ultimate goals of advanced neuroimaging techniques is their application at the single-subject level. A first study conducted using a support vector machine approach demonstrated 90% sensitivity and 100%

specificity in the diagnosis of PSP compared with Parkinson's disease and appears to be a very promising tool for future evaluation [62, 63].

The neuroimaging study of CBD and CBS is still challenging, since clinicopathologic correspondence is so poor [49, 64]. An autopsy study evaluated the neuroimaging features of either neuropathologically confirmed CBD patients or clinically diagnosed CBS patients with known histopathology [65]. CBD patients showed a common pattern of atrophy, involving left perirolandic and dorsal prefrontal cortices and striatum. However, even patients with CBS showed perirolandic atrophy irrespective of underlying pathology. From this perspective, perirolandic dysfunction, even if not specific for a single underlying pathology, is the fingerprint of both CBS and CBD [65, 66]. In addition, the analysis of white matter bundles in CBS supported this concept, showing a predominant involvement of long fronto-parietal associative fibers as well as sensorimotor projections of the cortical hand areas [67, 68].

Furthermore, an interesting study reported that the involvement of brain regions beyond the perirolandic region may predict the underlying pathology in CBS patients. In clinically defined CBS with CBD at autopsy, atrophy included also prefrontal cortex, whereas when brainstem and subcortical atrophy is more evident CBS-PSP could be suspected; finally, the extension of the pathology to posterior regions such as precuneus and temporo-parietal lobes are indicative of atypical presentation of AD pathology [65, 69, 70].

Along with structural neuroimaging, functional neuroimaging has been used to try to increase diagnostic accuracy. Dopamine receptor (DAT) imaging and [^{18}F]FDG-PET (fluorodeoxyglucose positron emission tomography) are promising tools in distinguishing PSP among parkinsonian disorders. Compared with Parkinson's disease, PSP patients showed more pronounced DAT losses in the anterior caudate, and anterior caudate/ventral

striatum ratio may help in differentiating PSP from Parkinson's disease [71]. Furthermore, [^{18}F]FDG-PET demonstrated metabolic differences within the clinical spectrum of PSP, with more evident fronto-thalamic impairment in PSP-RS than PSP-P [72].

When considering CBS/CBD, data are more heterogeneous, as once again the lack of autopsy confirmation of the CBS patients. Indeed, some CBS patients had DAT-positive, others DAT-negative findings [73]; thus this tool is not obviously useful in differential diagnosis.

Biomarkers for the diagnosis of PSP and CBD

One of the key issues in the management of neurodegenerative disorders is the requirement of reliable biomarkers to increase diagnostic accuracy, and to identify these distinctive 4R tauopathies beyond the clinical heterogeneous presentation. In the last few years, the experience in the Alzheimer field has been useful, and several biologic markers have been tested, with the attempt to identify reliable biologic changes reflecting the pathologic mechanisms of these disorders.

Since PSP and CBD are characterized by non-amyloid, non-synuclein tau pathology as a distinctive neuropathologic hallmark, the proposed biologic markers have mainly focused on tau, investigating quantitatively and qualitatively protein processing largely from cerebrospinal fluid (CSF) samples. Several studies aimed at evaluating tau levels in CSF in PSP and CBD/CBS patients compared with patients affected by either other tau-related disorders or other neurodegenerative extrapyramidal syndromes, such as synucleinopathies [74], but with no clear-cut results. Up to now, CSF tau levels along with CSF A β levels are useful to exclude AD

pathology in cases with atypical presentation, such as CBS, but no specific pattern of CSF biomarkers specific to the 4R tauopathies has been identified.

More recently, in CSF, extended (55 kDa) and truncated (33 kDa) tau forms have been recognized, and the tau 33 kDa/55 kDa ratio has been found to be reduced in PSP in comparison with other neurodegenerative disorders [75]. This marker needs further confirmation.

Conclusions

PSP and CBD represent a clinical challenge, because of their overlap with both FTD and parkinsonian syndromes. To improve diagnostic accuracy during life, international clinical consensus criteria have been established. However, despite these criteria, the correct diagnosis and the correct neuropathologic prediction is still unsatisfied and more work is warranted to improve the clinic pathologic relationship. Furthermore, although PSP and CBD share a common predominant composition of abnormal tau in 4 tandem repeats, the different pathologic mechanisms leading to these disorders still need to be elucidated.

Therapeutic strategies targeting tau hyperphosphorylation and other post-translational modifications, by promoting kinase inhibitors, or tau/microtubule stabilizers, are in development and will likely represent the future proper treatment for these orphan diseases.

References

1. Pick A. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prager Med Wochenschr* 1892;17:165–7.

-
2. von Braunmühl A. Pick'sche Krankheit. In: Bumke O, ed. *Handbuch der Geisteskrankheiten. Vol. 11. Part VII.* Berlin, Germany: Springer-Verlag. 1930;673–715. [German].
-
3. Akelaitis AJ. Atrophy of basal ganglia in Pick's disease. *Arch Neurol Psychiatry* 1944;**51**:27–34.
-
4. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brainstem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* 1964;**10**:333–59.
-
5. Rebeiz JJ, Kolodny EH, Richardson EP. Corticodentatonigral degeneration with neuronal achromasia. A progressive disorder of late adult life. *Trans Am Neurol Assoc* 1967;**9**:23–6.
-
6. Gibb WR, Luthert PJ, Marsden CD. Corticobasal degeneration. *Brain* 1989;**112**:1171–92.
-
7. Rebeiz JJ, Kolodny EH, Richardson EP Jr. Corticodentatonigral degeneration with neuronal achromasia. *Arch Neurol* 1968;**18**:20–33.
-
8. Constantinidis J, Richard J, Tissot R. Pick's disease. Histological and clinical correlations. *Eur Neurol* 1974;**11**(4):208–17.
-
9. Munoz-Garcia D, Ludwin SK. Classic and generalized variants of Pick's disease: a clinicopathological, ultrastructural, and immunocytochemical comparative study. *Ann Neurol* 1984;**16**(4):467–80.
-
10. Neary D, Snowden JS, Gustafson L, *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;**51**(6):1546–54.
-
11. The Lund and Manchester Groups. Consensus statement. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg*

Psychiatry 1994;**57**:416–18.

12. McKhann GM, Albert MS, Grossman M, *et al.* Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001;**58**:1803–9.

13. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain* 2005;**128**:1996–2005.

14. Spillantini MG, Goedert M. Tau mutations in familial frontotemporal dementia. *Brain* 2000;**123**:857–9.

15. Yamada T, McGeer PL, McGeer EG. Appearance of paired nucleated, tau-positive glia on patients with progressive supranuclear palsy brain tissue. *Neurosci Lett* 1992;**135**:99–102.

16. Feany MB, Dickson DW. Widespread cytoskeletal pathology characterizes corticobasal degeneration. *Am J Pathol* 1995;**146**(6):1388–96.

17. Komori T, Arai N, Oda M, *et al.* Astrocytic plaques and tufts of abnormal fibers do not coexist in corticobasal degeneration and progressive supranuclear palsy. *Acta Neuropathol* 1998;**96**(4):401–8.

18. Goedert M, Spillantini MG, Potier MC, Ulrich J, Crowther RA. Cloning and sequencing of the cDNA encoding an isoform of microtubule-associated protein tau containing four tandem repeats: differential expression of tau protein mRNAs in human brain. *EMBO J* 1989;**8**(2):393–9.

19. Goedert M, Wischik CM, Crowther RA, Walker JE, Klug A. Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau. *Proc Natl Acad Sci USA* 1988;**85**(11):4051–5.

20. Goode BL, Chau M, Denis PE, Feinstein SC. Structural and functional differences between 3-repeat and 4-repeat tau isoforms. Implications for normal

tau function and the onset of neurodegenerative disease. *J Biol Chem* 2000;**275**(49):38182–9.

21. Arai T, Ikeda K, Akiyama H, *et al.* Identification of amino-terminally cleaved tau fragments that distinguish progressive supranuclear palsy from corticobasal degeneration. *Ann Neurol* 2004;**55**(1):72–9.

22. Baker M, Litvan I, Houlden H, *et al.* Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet* 1999;**8**(4):711–15.

23. Di Maria E, Tabaton M, Vigo T, *et al.* Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. *Ann Neurol* 2000;**47**(3):374–7.

24. Pittman AM, Myers AJ, Abou-Sleiman P, *et al.* Linkage disequilibrium fine mapping and haplotype association analysis of the tau gene in progressive supranuclear palsy and corticobasal degeneration. *J Med Genet* 2005;**42**(11):837–46.

25. Rademakers R, Melquist S, Cruts M, *et al.* High-density SNP haplotyping suggests altered regulation of tau gene expression in progressive supranuclear palsy. *Hum Mol Genet* 2005;**14**(21):3281–92.

26. Schellenberg GD. A genome-wide association study of progressive supranuclear palsy and corticobasal degeneration: genes that modify risk. *Dement Geriatr Cogn Disord* 2010;**30**(Suppl 1):18–19.

27. Donker Kaat L, Boon AJ, Azmani A, *et al.* Familial aggregation of parkinsonism in progressive supranuclear palsy. *Neurology* 2009;**73**(2):98–105.

28. Borroni B, Goldwurm S, Cerini C, *et al.* Familial aggregation in progressive supranuclear palsy and corticobasal syndrome. *Eur J Neurol* 2011;**18**(1):195–7.

29. Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive

supranuclear palsy and multiple system atrophy: a cross sectional study. *Lancet* 1999;**354**:1771–5.

30. Armstrong MJ, Litvan I, Lang AE, *et al.* Criteria for the diagnosis of corticobasal degeneration. *Neurology* 2013;**80**(5):496–503.

31. Litvan I, Agid Y, Calne D, *et al.* Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 1996;**47**(1):1–9.

32. Boeve BF. Progressive supranuclear palsy. *Parkinsonism Relat Disord* 2012;**18**(Suppl 1):S192–4.

33. Rohrer JD, Lashley T, Schott JM, *et al.* Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain* 2011;**134**:2565–81.

34. Dickson DW, Kouri N, Murray ME, Josephs KA. Neuropathology of frontotemporal lobar degeneration-tau (FTLD-tau). *J Mol Neurosci* 2011;**45**(3):384–9.

35. Wakabayashi K, Takahashi H. Pathological heterogeneity in progressive supranuclear palsy and corticobasal degeneration. *Neuropathology* 2004;**24**(1):79–86.

36. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol* 2009;**8**(3):270–9.

37. Osaki Y, Ben-Shlomo Y, Lees AJ, *et al.* Accuracy of clinical diagnosis of progressive supranuclear palsy. *Mov Disord* 2004;**19**(2):181–9.

38. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* 2002;**125**:861–70.

-
- 39.** Litvan I. Recent advances in atypical parkinsonian disorders. *Curr Opin Neurol* 1999;**12**(4):441–6.
-
- 40.** Wadia PM, Lang AE. The many faces of corticobasal degeneration. *Parkinsonism Relat Disord* 2007;**13**(Suppl 3):S336–40.
-
- 41.** Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Ann Neurol* 2003;**54**(Suppl 5):S15–19.
-
- 42.** Riley DE, Lang AE, Lewis A, *et al.* Cortical-basal ganglionic degeneration. *Neurology* 1990;**40**:1203–12.
-
- 43.** Lang AE, Riley DE, Bergeron C. Cortical-basal ganglionic degeneration. In: Calne DB, ed. *Neurodegenerative Diseases*. Philadelphia: W.B. Saunders. 1994;877–94.
-
- 44.** Watts RL, Mirra SS, Richardson EP. Cortical-basal ganglionic degeneration. In: Marsden CD, Fahn S, eds. *Movement Disorders, Vol 3*. Oxford: Butterworth Heinemann. 1994;282–99.
-
- 45.** Kumar R, Bergeron C, Pollanen M, Lang AE. Cortical-basal ganglionic degeneration. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease & Movement Disorders*. Baltimore: Williams & Wilkins. 1998;297–316.
-
- 46.** Litvan I, Cummings JL, Mega M. Neuropsychiatric features of corticobasal degeneration. *J Neurol Neurosurg Psychiatry* 1998;**65**:717–21.
-
- 47.** Bak TH, Hodges JR. Corticobasal degeneration: clinical aspects. *Handb Clin Neurol* 2008;**89**:509–21.
-
- 48.** Hodges JR, Davies RR, Xuereb JH, *et al.* Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* 2004;**56**(3):399–406.
-
- 49.** Josephs KA, Petersen RC, Knopman DS, *et al.* Clinicopathologic analysis

of frontotemporal and corticobasal degenerations and PSP. *Neurology* 2006;**66**(1):41–8.

50. McMonagle P, Blair M, Kertesz A. Corticobasal degeneration and progressive aphasia. *Neurology* 2006;**67**(8):1444–51.

51. Massey LA, Micallef C, Paviour DC, *et al.* Conventional magnetic resonance imaging in confirmed progressive supranuclear palsy and multiple system atrophy. *Mov Disord* 2012;**27**(14):1754–62.

52. Massey LA, Jäger HR, Paviour DC, *et al.* The midbrain to pons ratio: a simple and specific MRI sign of progressive supranuclear palsy. *Neurology* 2013;**80**(20):1856–61.

53. Quattrone A, Nicoletti G, Messina D, *et al.* MR imaging index for differentiation of progressive supranuclear palsy from Parkinson disease and the Parkinson variant of multiple system atrophy. *Radiology* 2008;**246**(1):214–21.

54. Borroni B, Malinverno M, Gardoni F, *et al.* A combination of CSF tau ratio and midsagittal midbrain-to-pons atrophy for the early diagnosis of progressive supranuclear palsy. *J Alzheimers Dis* 2010;**22**(1):195–203.

55. Cosottini M, Ceravolo R, Faggioni L, *et al.* Assessment of midbrain atrophy in patients with progressive supranuclear palsy with routine magnetic resonance imaging. *Acta Neurol Scand* 2007;**116**(1):37–42.

56. Duchesne S, Rolland Y, Vérin M. Automated computer differential classification in parkinsonian syndromes via pattern analysis on MRI. *Acad Radiol* 2009;**16**(1):61–70.

57. Shi HC, Zhong JG, Pan PL, *et al.* Gray matter atrophy in progressive supranuclear palsy: meta-analysis of voxel-based morphometry studies. *Neurol Sci* 2013;**34**(7):1049–55.

58. Padovani A, Borroni B, Brambati SM, *et al.* Diffusion tensor imaging and

voxel based morphometry study in early progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 2006;**77**(4):457–63.

59. Price S, Paviour D, Scahill R, *et al.* Voxel-based morphometry detects patterns of atrophy that help differentiate progressive supranuclear palsy and Parkinson's disease. *Neuroimage* 2004;**23**(2):663–9.

60. Agosta F, Kostić VS, Galantucci S, *et al.* The in vivo distribution of brain tissue loss in Richardson's syndrome and PSP-parkinsonism: a VBM-DARTEL study. *Eur J Neurosci* 2010;**32**(4):640–7.

61. Agosta F, Pievani M, Svetel M, *et al.* Diffusion tensor MRI contributes to differentiate Richardson's syndrome from PSP-parkinsonism. *Neurobiol Aging* 2012;**33**(12):2817–26.

62. Focke NK, Helms G, Scheewe S, *et al.* Individual voxel-based subtype prediction can differentiate progressive supranuclear palsy from idiopathic Parkinson syndrome and healthy controls. *Hum Brain Mapp* 2011;**32**(11):1905–15.

63. Sajjadi SA, Acosta-Cabronero J, Patterson K, *et al.* Diffusion tensor magnetic resonance imaging for single subject diagnosis in neurodegenerative diseases. *Brain* 2013;**136**:2253–61.

64. Ling H, O'Sullivan SS, Holton JL, *et al.* Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain* 2010;**133**:2045–57.

65. Lee SE, Rabinovici GD, Mayo MC, *et al.* Clinicopathological correlations in corticobasal degeneration. *Ann Neurol* 2011;**70**(2):327–40.

66. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron* 2009;**62**(1):42–52.

67. Borroni B, Garibotto V, Agosti C, *et al.* White matter changes in

corticobasal degeneration syndrome and correlation with limb apraxia. *Arch Neurol* 2008;**65**(6):796–801.

68. Erbetta A, Mandelli ML, Savoirdo M, *et al.* Diffusion tensor imaging shows different topographic involvement of the thalamus in progressive supranuclear palsy and corticobasal degeneration. *Am J Neuroradiol* 2009;**30**(8):1482–7.

69. Whitwell JL, Jack CR Jr, Boeve BF, *et al.* Imaging correlates of pathology in corticobasal syndrome. *Neurology* 2010;**75**(21):1879–87.

70. Borroni B, Premi E, Agosti C, *et al.* CSF Alzheimer's disease-like pattern in corticobasal syndrome: evidence for a distinct disorder. *J Neurol Neurosurg Psychiatry* 2011;**82**(8):834–8.

71. Oh M, Kim JS, Kim JY, *et al.* Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. *J Nucl Med* 2012;**53**(3):399–406.

72. Srulijes K, Reimold M, Liscic RM, *et al.* Fluorodeoxyglucose positron emission tomography in Richardson's syndrome and progressive supranuclear palsy-parkinsonism. *Mov Disord* 2012;**27**(1):151–5.

73. Ceravolo R, Rossi C, Cilia R, *et al.* Evidence of delayed nigrostriatal dysfunction in corticobasal syndrome: a SPECT follow-up study. *Parkinsonism Relat Disord* 2013;**19**(5):557–9.

74. Urakami K, Wada K, Arai H, *et al.* Diagnostic significance of tau protein in cerebrospinal fluid from patients with corticobasal degeneration or progressive supranuclear palsy. *J Neurol Sci* 2001;**183**(1):95–8.

75. Borroni B, Malinverno M, Gardoni F, *et al.* Tau forms in CSF as a reliable biomarker for progressive supranuclear palsy. *Neurology* 2008;**71**(22):1796–803.

76. Bugiani O, Murrell JR, Giaccone G, *et al.* Frontotemporal dementia and corticobasal degeneration in a family with a P301S mutation in tau. *J*

Neuropathol Exp Neurol 1999;**58**(6):667–77.

77. Poorkaj P, Muma NA, Zhukareva V, *et al.* An R5L tau mutation in a subject with a progressive supranuclear palsy phenotype. *Ann Neurol* 2002;**52**(4):511–16.

78. Pastor P, Pastor E, Carnero C, *et al.* Familial atypical progressive supranuclear palsy associated with homozygosity for the delN296 mutation in the tau gene. *Ann Neurol* 2001;**49**(2):263–7.

79. Ferrer I, Pastor P, Rey MJ, *et al.* Tau phosphorylation and kinase activation in familial tauopathy linked to delN296 mutation. *Neuropathol Appl Neurobiol* 2003;**29**(1):23–34.

80. Oliva R, Pastor P. Tau gene delN296 mutation, Parkinson's disease, and atypical supranuclear palsy. *Ann Neurol* 2004;**55**(3):448–9.

81. Rossi G, Gasparoli E, Pasquali C, *et al.* Progressive supranuclear palsy and Parkinson's disease in a family with a new mutation in the tau gene. *Ann Neurol* 2004;**55**(3):448.

82. Rojo A, Pernaute RS, Fontán A, *et al.* Clinical genetics of familial progressive supranuclear palsy. *Brain* 1999;**122**:1233–45.

83. Ros R, Thobois S, Streichenberger N, *et al.* A new mutation of the tau gene, G303V, in early-onset familial progressive supranuclear palsy. *Arch Neurol* 2005;**62**(9):1444–50.

Section 3



Approach to the diagnosis of FTD

Chapter 8

Overview of clinical assessment of frontotemporal dementia syndromes



Bradford C. Dickerson, Simon Ducharme, and Chiadi U. Onyike

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

Description of the clinical phenotypes of frontotemporal lobar degeneration (FTLD) has a complex history dating back over 100 years, as reviewed in detail in [Chapter 1](#). Clinical neuropsychiatry continues to influence our approach to the evaluation of patients with clinical syndromes suspected to be associated with FTLD pathology. Clinicopathologic and genetic advances in our understanding of FTLD, and rapid growth in our application of neuroimaging and physiochemical assays to the study of FTLD in the last 15 years has assisted and complicated the clinical assessment of individual patients. This chapter provides an overview of an approach to the clinical

assessment of patients with suspected FTLD, drawing heavily on the clinical practice of the authors.

Arnold Pick, Paul Serieux, and other pioneers in neuropsychiatry provided insightful descriptions of the insidious and focal changes in the areas of conduct, personality, and language, alongside relative preservation of memory and orientation, that characterize most presentations of FTLD (Berrios and Girling, [1994](#)). These concepts are largely retained today. FTLD is understood to be a loosely knit group of neurodegenerative diseases that primarily affect the frontal and anterior temporal lobes, with relative sparing of other cortical regions. FTLD frequently features subcortical degeneration as well, involving the basal ganglia and, in some cases, the basal forebrain and brainstem nuclei. On the other hand, present-day terminology for FTLD diseases and phenotypes remains unwieldy and confusing. [Table 8.1](#) shows a glossary of these terms; we use the umbrella term “frontotemporal dementia (FTD)” to refer to the principal phenotypes – “behavioral variant FTD (bvFTD)” and the “primary progressive aphasias (PPA).” PPA in turn encompasses “semantic dementia” (SD, or the semantic variant of PPA [svPPA]), the “non-fluent or agrammatic variant of PPA,” and the “logopenic” variant of PPA. In addition, the overlap with neurodegenerative motor syndromes including progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and amyotrophic lateral sclerosis (ALS) has led to the concept of motor phenotypes of FTLD spectrum. Although clinicopathologic relationships along this spectrum are highly complex, some themes are beginning to emerge and are illustrated in [Figure 8.1](#).

Table 8.1 Glossary of terms describing the frontotemporal dementias

Term	Acronym	Description
------	---------	-------------

Frontotemporal lobar degeneration	FTLD	Refers collectively to the FTLD neurodegenerative pathologies (“the diseases”) that underlie all the clinical phenotypes; see Chapter 13
Frontotemporal dementia	FTD	An umbrella term for the behavioral and language phenotypes typically associated with one of the FTLD pathologies
Behavioral variant frontotemporal dementia	bvFTD	Refers to a clinical phenotype featuring primarily disordered conduct, temperament, and judgment; see Chapter 4
Primary progressive aphasia	PPA	Refers to the group of phenotypes characterized primarily by focal aphasia; see Chapter 5
Progressive non-fluent aphasia	PNFA	Refers to the phenotype mainly characterized by impaired production and grammatical structure of speech; often referred to now as the non-fluent/agrammatic variant of PPA (nfvPPA or PPA-g); see Chapter 5
Semantic dementia	SD	Refers to the phenotype mainly characterized by focal loss of word and object knowledge; often referred to now as the semantic variant of PPA (svPPA); see Chapter 5
Logopenic progressive aphasia	LPA	Refers to the phenotype mainly characterized by dysnomia and impaired speech composition; often referred to now as the logopenic variant of PPA (lvPPA or PPA-l); see Chapter 5

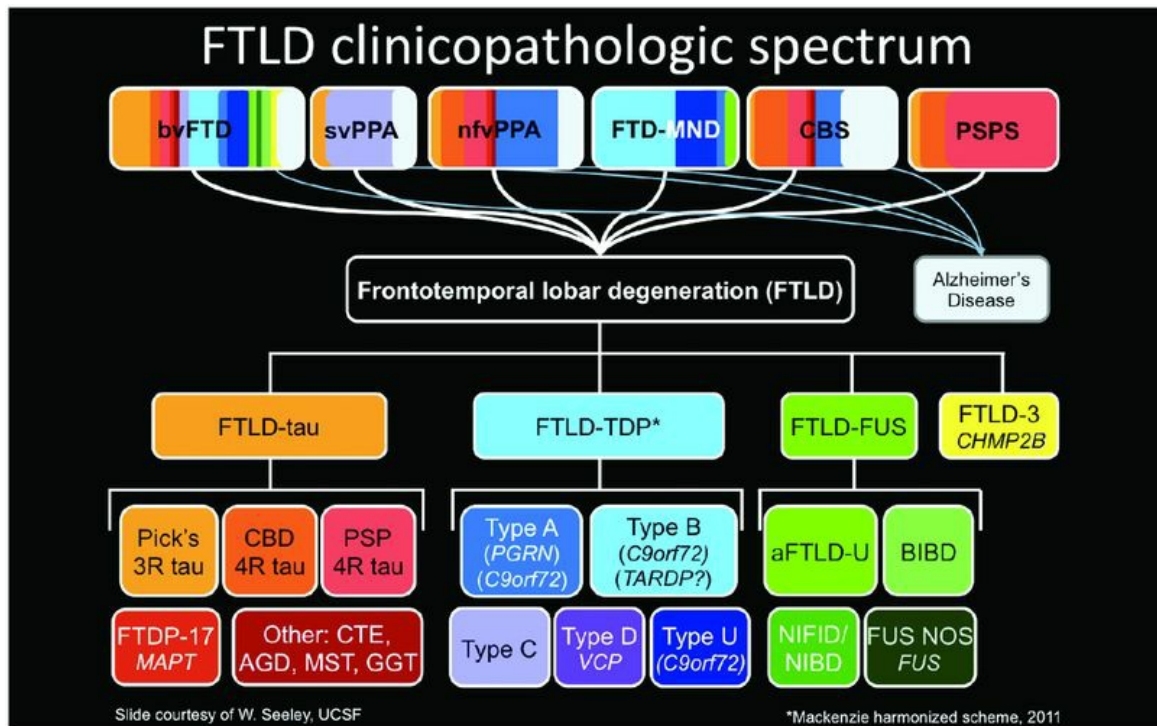


Figure 8.1 The complexity of clinicopathologic relationships along the frontotemporal lobar degeneration (FTLD) spectrum. The major clinical syndromes along the FTLD spectrum are shown in the top row of the slide, and the pathologic diseases are shown below. The width of the colored bar in each clinical syndrome represents the approximate percentage of that syndrome that has been associated with each color-coded pathology below. All of the pathologies under the Frontotemporal lobar degeneration (FTLD) heading are described in detail in [Chapter 13](#). A portion of most of the clinical syndromes may be attributed to Alzheimer's disease pathology (shown in white). For example, the majority of cases of svPPA are associated with FTLD-TDP43 type C pathology (lavender), while the majority of PSPS cases are due to PSP 4R tauopathy (salmon). Abbreviations: bvFTD = behavioral variant frontotemporal dementia, svPPA = semantic variant primary progressive aphasia, nvfPPA = non-fluent variant PPA, FTD-MND = FTD-motor neuron disease, CBS = corticobasal syndrome, PSPS = progressive supranuclear palsy syndrome, FTLD-tau = tau-positive FTLD, FTLD-TDP = FTLD with TDP-43 (transactive response DNA-binding protein 43) proteinopathy, FTLD-FUS = FTLD with fused in sarcoma accumulation, CBD = corticobasal degeneration, PSP = progressive supranuclear palsy,

aFTLD-U = atypical FTLD with ubiquitin inclusion, BIBD = basophilic inclusion body disease, FTDP-17 = frontotemporal dementia with parkinsonism-17, CTE = chronic traumatic encephalopathy, AGD = argyrophilic grain disease, MST = multisystem tauopathy, GGT = globular glial tauopathy, NIFID = neuronal intermediate filament inclusion disease, NIBD = neurofilament inclusion body disease, NOS = not otherwise specified.

Figure used with appreciation, courtesy of W.W. Seeley, UCSF, San Francisco, CA, based on Mackenzie harmonized scheme, 2011.

For most of the twentieth century, progressive dementias in which deteriorating judgment and conduct were the most salient features were diagnosed “Pick's disease.” The histopathologic diversity of FTLD was highlighted in 1974 (Constantinidis *et al.*, [1974](#)), and followed soon afterwards by Elizabeth Warrington's seminal description of focal word and object agnosia (Warrington, [1975](#)), which culminated in the description of SD in 1989 (Snowden *et al.*, [1989](#)). Starting in 1982 with a clinicopathologic report of six cases, Marsel Mesulam reinvigorated interest in PPA (Mesulam, [1982](#)). Since the 1980s, FTD has been captured in formal diagnostic criteria, beginning with descriptive studies from the Lund (Gustafson, [1987](#)) and Manchester (Neary *et al.*, [1988](#)) groups that renewed interest in the behavioral phenotype of FTD and culminated in clinical and pathologic diagnostic criteria (Brun *et al.*, [1994](#)). These were followed several years later by more formalized clinical rules specifying three subtypes characterized by disruption of conduct, temperament, and socialization; progressive non-fluent aphasia; or progressive semantic aphasia and associative agnosia (SD) (Neary *et al.*, [1998](#)). These diagnostic criteria presented rigid core and peripheral criteria for the syndromes, and thus were rather complex. Simpler criteria proposed in 2001 (McKhann *et al.*, [2001](#)) emphasized ease of use, by stipulating that FTLD is characterized

by early and progressive changes in personality or language of sufficient severity to cause functional disability. These criteria did not gain wide acceptance, owing to a perception of operational vagueness. The contemporary criteria, developed in 2011 for the behavioral (Rascovsky *et al.*, [2011](#)) and aphasia (Gorno-Tempini *et al.*, [2011](#)) phenotypes, have brought flexible application (which accommodates the diversity of presentations), established a hierarchy of diagnostic confidence (i.e., “possible,” “probable,” or “definite” bvFTD), and also incorporated neuroimaging features, as well as genetic and neuropathologic typing into the diagnostic process. These latest criteria have been incorporated, in simplified form, into DSM-5 (American Psychiatric Association, [2013a](#)).

Demographic distribution of FTLT is an important consideration in the clinical assessment. FTLT usually manifests in midlife, i.e., in patients who are 45–65 years old, although cases developing at ages as young as 21 (Snowden *et al.*, [2004](#)) and as old as 85 (Gislason *et al.*, [2003](#)) have been reported. The majority of cases in many bvFTD case series are male, whereas the aphasia phenotypes appear to have an even sex distribution. Age at presentation may also influence the presenting phenotype (Velakoulis *et al.*, [2009](#)), with younger cases showing a more “psychiatric” presentation, and elders a mainly “cognitive” presentation. Epidemiologic studies have also proposed that age-related phenotypic variation is a cause of under-ascertainment of cases (Ibach *et al.*, [2003](#)), noting that FTLT may be more common than is recognized among the elderly (Knopman *et al.*, [2004](#); Borroni *et al.*, [2010](#)) where amnesic presentations are frequently seen and mistaken for Alzheimer's disease (AD) (Baborie *et al.*, [2012](#); Onyike *et al.*, [2013](#)).

Clinical characteristics of FTLT

spectrum diseases

FTLD phenotypes are, as noted in earlier chapters, largely determined by the distribution of neurodegeneration – i.e., by particular patterns of frontotemporal or frontostriatal circuit dysfunction as a result of degenerative pathology. The regional patterns are, at least in some cases, related in part to the underlying histopathologic types (Rohrer *et al.*, [2010](#); Whitwell *et al.* [2012a](#)). Symptoms referable to extrapyramidal, brainstem, and upper/lower motor neuron systems are commonly seen because degeneration affects these areas in many cases. Ultimately phenotypes are stereotypical in most respects, being correlated with typical atrophy patterns (seen as brain imaging signatures) that may be linked at least probabilistically to histopathologic types. This forms the basis for differential diagnosis, such that a case of bvFTD or PPA with accompanying parkinsonian symptoms will be differentiated from idiopathic Parkinson's disease (PD) because the clinical features (behavioral and/or language) will extend well beyond and dominate the clinical phenotype. Furthermore, the patient may manifest motor features that are not part of typical parkinsonism, such as gait apraxia. That is, a wide range of clinical phenomena can accompany the typical features of FTLD syndromes. The clinician should not be discouraged by this complexity; we have learned that as experience with the FTLD syndromes grows, one's diagnostic behavior shifts imperceptibly from a synthetic to a (faster) pattern recognition process. At the same time, ambiguous cases are not uncommon so it is important to have a firm grounding in the symptoms and signs that signal FTLD, the laboratory data that confirm or discount the diagnosis, and the less formal “rules of thumb,” “red flags,” and caveats that may help in resolving ambiguous cases. We will first briefly touch on the major FTLD clinical syndromes and then discuss their differential diagnosis.

Major FTLN clinical syndromes

bvFTD appears to be the most common variant of FTLN. Its essence is a disruption of conduct, temperament, judgment, self-control, and socialization, with heterogeneity in symptom combinations according to the distribution of degeneration in pertinent brain systems. The typical features and their variations are reviewed in [Chapters 2, 3, and 4](#).

The progressive aphasia phenotypes – non-fluent/agrammatic, semantic, and logopenic – feature focal disruptions of language in symptom combinations that are discussed in detail in [Chapter 5](#).

Many investigators increasingly view conditions with prominent motor symptoms as falling within the FTLN spectrum. These include PSP and CBS, reviewed in detail in [Chapter 7](#), and ALS, reviewed in detail in [Chapter 6](#).

Other clinical phenotypes

Attention has been drawn to a variety of uncommon clinical phenotypes associated with FTLN spectrum pathology or with causal mutations. These include atypical “neurologic” presentations, such as posterior cortical atrophy or AD-like presentations. It is becoming increasingly recognized that FTD patients with *GRN* mutations have more parietal involvement than typical FTD patients (Masellis *et al.*, [2006](#); Whitwell *et al.*, [2007](#), [2012b](#); Le Ber *et al.*, [2008](#)). In some cases, this is an early presenting feature and is associated with prominent early limb apraxia or visuospatial dysfunction. We have seen one case of FTLN-TDP type A due to a *GRN* mutation that presented as a classic case of posterior cortical atrophy with lateralized visual impairment and topographic disorientation. It is also clear that, despite the exclusion criterion of episodic memory impairment in the new diagnostic criteria for both bvFTD and PPA (which is important from a

research perspective), some patients with FTD exhibit prominent episodic memory impairment (Hornberger *et al.*, [2010](#), [2012](#)). Thus, clinicians should keep in mind that not every patient with PPA or bvFTD will have preserved episodic memory and visuospatial function.

Atypical “psychiatric” presentations of FTLD are seen, usually featuring states such as mania, depression, obsessive–compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), and psychosis. Another entity, designated “FTD phenocopy,” has been described. These are cases who present with a full complement of symptoms and signs, and an overall clinical appearance, that is consistent with (and meets criteria for) a bvFTD diagnosis but shows little neuropsychological dysfunction and brain imaging abnormality (Davies *et al.*, [2006](#); Kipps *et al.*, [2007](#); Hornberger *et al.*, [2009](#)) and little (if any) progression over a number of years. This causes, in time, uncertainty about the validity of a neurodegenerative explanation of the case. Some investigators believe these individuals have a primary psychiatric diagnosis, such as Asperger syndrome or other developmental syndrome (Hornberger *et al.*, [2009](#)). Yet, despite the imperceptible or slow progression, in some of these patients post-mortem brain examination demonstrates FTLD pathology (Brodtmann *et al.*, [2013](#)). Furthermore, FTD phenocopy patients known to be carriers of the *C9orf72* gene mutation associated with FTD (Khan *et al.*, [2012](#)) are considered true variants of FTLD.

Differential diagnosis of FTLD

Several other chapters in this volume review differential diagnosis, including [Chapters 2](#) and [3](#), which discuss differentiating FTLD from AD, dementia with Lewy bodies (DLB), vascular dementia (VaD), prion

diseases, and psychiatric phenocopies. In this chapter we describe general principles in the differential diagnosis of FTLN to attempt to illustrate the process of making an FTLN diagnosis. We also consider a variety of confounders and mimics, some of them rather rare. We aim here to emphasize that clinicians consider a broad swath of conditions when the clinical presentation suggests an FTLN syndrome but is also ambiguous, or when laboratory or neuroimaging investigations include unexpected findings.

Differential diagnosis with diseases traditionally considered “neurologic”

The differential diagnosis of dementia generally includes toxic-metabolic conditions, including anemia, vitamin B12 deficiency, and thyroid, liver, or renal disease. Infectious or inflammatory processes can be a consideration as well. For the most part, these conditions do not produce clinical syndromes overlapping with prototypical bvFTD or PPA, but should always be considered when clinical features are atypical.

Especially in unusually young or unusually rapidly progressive cases, it is worth considering one of the rapidly progressive dementias (RPD), including Creutzfeldt–Jakob disease (which usually progresses to death within 6–12 months) or other prion diseases, viral encephalitis, primary central nervous system vasculitis, paraneoplastic syndromes, or other autoimmune encephalopathies; assessment with a paraneoplastic and vasculitis panel is valuable in these cases.

In young adulthood or even middle age, lipid-storage disorders or white matter degenerative diseases may present with behavioral disturbance and cognitive decline. There are often accompanying features such as retinopathy or organomegaly (e.g., liver or spleen). Mitochondrial disorders

may sometimes be included in the differential diagnosis, especially if there are paroxysmal symptoms or accompanying clinical features in the patient and/or maternal family members, including short stature, hearing loss, cardiac conduction loss, diabetes, or retinal disease.

Degenerative basal ganglia disorders can begin with prominent behavioral syndromes. Huntington's disease often starts as a neuropsychiatric syndrome with obsessive–compulsive and manic symptoms and loss of executive control. Family history should be informative but may be misleading if parental life-span was short or the pedigree is small. Wilson's disease should be considered in young patients with neuropsychiatric symptoms, in which case a workup for abnormalities of copper metabolism would be appropriate.

Normal pressure hydrocephalus (NPH) is a controversial entity (e.g., McGirr *et al.*, [2013](#)) but should be a consideration, especially in patients with early incontinence, gait disturbance, and a frontal systems behavioral syndrome involving predominantly apathy. In his seminal study of a series of cases of patients with NPH, Raymond Adams ([1966](#)) concluded the following: “We watched for [NPH] particularly amongst the patients suspected of having a dementing degenerative disease and found that those in whom poor memory, psychomotor impairment, uncertainty of gait and sphincteric incontinence were early symptoms, and where the evolution of the illness occurred over a few weeks to months and fluctuated, should be suspected as having hydrocephalus rather than presenile or senile brain atrophy.” A prior history of head trauma, subarachnoid hemorrhage, or meningitis increases the suspicion of NPH. Structural neuroimaging should reveal enlarged ventricles in the relative absence of atrophy; in some cases, additional neuroimaging including specialized magnetic resonance imaging (MRI) sequences or fluorodeoxyglucose positron emission tomography (FDG-PET) can also be helpful.

At some hospitals, a three-day lumbar drain trial with repeat cognitive-motor assessments has replaced large-volume cerebrospinal fluid (CSF) collection via lumbar puncture as the assessment for ventriculoperitoneal shunt responsiveness; at the same time, CSF can be examined for other processes including AD-related proteins if AD is suspected. In some cases, shunt treatment can provide meaningful clinical improvement.

The “sagging brain syndrome” is a recently recognized condition thought to involve a chronic CSF leak with downward displacement of brain structures and a cognitive-behavioral syndrome involving frontal systems dysfunction and in some cases symptoms similar to bvFTD. Daytime somnolence and headache are often present. All eight patients in the original report showed evidence of frontotemporal hypometabolism on FDG-PET scans (Wicklund *et al.*, [2011](#)). Identifying the CSF leak is the key to targeted intervention. Some patients improve with treatment including epidural blood patch. Although rare, this condition may be at least partly reversible and so is an important reason to obtain neuroimaging studies in patients with frontal behavioral syndromes.

In our experience, some patients who turn out to be diagnosed with FTD may be thought to have a temporal lobe seizure disorder because of the development of hypergraphia and hyperreligiosity, as well as elevated mood. More commonly, patients with seizure disorders and progressive personality or behavioral changes are suspected of possibly having FTD but in our experience do not exhibit typical symptoms, progressive decline, or typical imaging abnormalities.

Differential diagnosis with diseases traditionally considered “psychiatric”

Patients with FTD are much more likely than those with other neurodegenerative diseases to have received an initial diagnosis of a psychiatric disorder, most commonly depression or bipolar affective disorder, but occasionally schizophrenia (Woolley *et al.*, [2011](#)), OCD, or ADHD. There are, however, important differences in behavior between patients with FTD and those with psychiatric conditions. In FTD, it is unusual for patients to complain of sadness or despair, of anxiety, or indeed to acknowledge any suffering or handicap. Patients with FTD are generally unlikely to notice and regret functional decline, or to show remorse for offensive behavior whereas patients with primary psychiatric states will (with the exception of many with psychosis). In healthcare consultations the spontaneous behavior of FTD patients has been found to differ from that of patients with psychiatric conditions: verbal or physical interruption of the consultation occurred more often in patients with SD and a lack of concern for the clinician's expectations was more common in FTD patients (Rankin *et al.*, [2008](#)). In our experience, FTLD patients have reached into pockets, attempted to comb the examiner's hair, sat on the examiner's table or in the examiner's chair, and searched for food in the office.

The frequent occurrence of psychotic symptoms in carriers of the *C9orf72* mutation merits specific attention. Based on reports from several large series (Dobson-Stone *et al.*, [2012](#); Kertesz *et al.*, [2013](#)), a substantial minority of *C9orf72* mutation carriers present with a psychotic symptom or syndrome, compared with < 4 % of non-mutation carriers (Snowden *et al.*, [2012](#)). These states have included florid mono-delusional psychosis, and bizarre irrational behavior. Not surprisingly, these patients received psychiatric treatment well before referral for neurologic or neuropsychiatric examination. Thus psychosis appearing during or after the fourth decade of life, particularly if characterized by florid mono-delusional beliefs, should arouse suspicion of FTLD and warrants neuropsychiatric consultation.

Likewise, psychosis presenting in association with motor phenomena, such as parkinsonism or limb or gait apraxia, should arouse suspicion.

In our experience, many patients eventually determined to have bvFTD, PPA, PSP, or CBS were earlier diagnosed with and treated for depression. Usually apathy and social or occupational withdrawal have been interpreted as a depressive state, and the severity of dysfunction coupled with a dearth of identifiable triggers (social or environmental) prompts a diagnosis of major depression. It should be noted that symptoms seen in major depressive disorder (MDD) such as lack of interest, decreased motivation, anergia, sleep disruption, and impaired concentration (American Psychiatric Association, [2013b](#)) are also observed in FTD. MDD may be distinguished from bvFTD by inquiring about sadness, despair, guilty ruminations, feelings of worthlessness, and suicidal thoughts, symptoms that typically would not appear in FTD (and are thus unlikely to occur together). When sadness is observed in bvFTD or more often PPA, it usually is reactive and linked to an identifiable problem.

Some patients with bvFTD may appear manic and may be diagnosed with bipolar disorder. In particular, the disinhibition and social judgment deficits can overlap with those observed in manic episodes (Woolley *et al.*, [2007](#)). Other common manic symptoms can also be seen in bvFTD, including irritability, distractibility, risk-taking behavior, socially inappropriate behaviors, impaired judgment, and excessive involvement in pleasurable activities with potentially harmful consequences (e.g., compulsive purchases, gambling). Although patients with bvFTD can be inappropriately jocular (Perry and Miller, [2001](#)), patients with euphoric mania have a qualitatively distinct elevated and expansive mood, accompanied by a sense of grandiosity and invulnerability that is uncommon in bvFTD. Individuals with bvFTD also rarely report racing thoughts typically seen in mania, although distractibility could lead to apparent flight

of ideas. Most importantly, bvFTD involves an inexorable deterioration of cognitive functions over time, while bipolar disorder is usually an episodic syndrome. Severe cases of bipolar disorder can evolve toward a chronic manic or depressive state, but cognitive impairment is generally not as profound or progressive (Mann-Wrobel *et al.*, [2011](#)).

Further complicating the differential diagnosis of bvFTD versus bipolar disorder, there are a few case reports of autosomal dominant bvFTD preceded by a prodrome of many years of symptoms compatible with primary bipolar disorder. These include dementia secondary to *GRN* mutations (Cerami *et al.*, [2011](#)) and *C9orf72* hexanucleotide repeat expansion (Floris *et al.*, [2013](#); Meisler *et al.*, [2013](#)). Given that the phenomenologic presentation was identical to bipolar disorder in those cases, a careful family history of FTD or ALS should be performed in patients with late-onset mania, and genetic testing for *C9orf72/GRN* considered. Conversely, a family history of late-onset mania in a proband with bvFTD might have to be considered as an autosomal dominant mutation. In light of these findings, a genetic link between bipolar disorder and FTD has been suggested, although the rate of *C9orf72* mutations in individuals with primary bipolar disorder appears low (Meisler *et al.*, [2013](#)).

OCD may be important to consider in the differential diagnosis, since perseverative, stereotyped, and compulsive/ritualistic behaviors are common in FTD (38–78%), particularly bvFTD and SD (Ames *et al.*, [1994](#); Mendez *et al.*, [2005](#)). These range from simple stereotypies such as rubbing and tapping, to more complex and elaborate rituals mimicking compulsions typical of OCD (e.g., checking, washing, counting) (Mendez *et al.*, [2005](#)). Cases of late-onset compulsions as the initial manifestation of bvFTD (Mendez *et al.*, [1997](#); Nakaaki *et al.* [2007b](#)) and SD (Pompanin *et al.*, [2012](#)) have also been reported.

Given that compulsive behaviors can be similar in bvFTD and OCD, attention should be directed to the qualitative nature of obsessional ideas. Obsessions are recurrent thoughts, urges, or images experienced as intrusive and unwanted, which lead to anxiety and distress. In OCD, the majority of patients engage in repetitive rituals as a response to their obsessions (American Psychiatric Association, [2013b](#)). Behaviors are performed either to reduce distress associated with obsessions, or to prevent an adverse outcome (although there is usually a limited realistic connection between the ritual and the actual outcome). In our experience, patients with FTD and compulsive behaviors typically do not report obsessions – although family members may describe fixations with food, TV programs, cleanliness, object arrangements, and such like that may drive specific compulsions such as food searching, compulsive programming, and so on. Generally, however, FTLT patients usually do not describe or may flatly deny suffering from obsessive thoughts (Ames *et al.*, [1994](#)). It has not been established whether obsessions are indeed absent or whether patients do not have sufficient insight to observe, or lack the capacity to articulate their thoughts in order to report them to clinicians. In those SD patients with the most complex rituals (Modirrousta *et al.*, [2013](#)), a loss of semantic memory might result in an inability to conceptualize or verbalize obsessions.

Hoarding disorder is an OCD-related disorder introduced to the psychiatry lexicon in DSM-5 (American Psychiatric Association, [2013b](#)). It is common in FTD (Mendez and Shapira, [2008](#)), where it may be one of the first symptoms (Nakaaki *et al.*, [2007b](#)). Idiopathic hoarding tends to start in early life, and gets worse over the years. In FTD, hoarding behavior usually follows the onset of cognitive decline, and compared with primary hoarding is associated with less anxiety about the need to save items, and less distress about discarding them. Objects collected by hoarders tend to have at least some theoretical value (e.g., newspapers, clothes, paperwork), and

patients usually endorse at least some, often albeit weak, rationale regarding potential use. Items accumulated by patients with FTD can be unsanitary (e.g., rotten food, urine); some authors conceptualize this collecting behavior as secondary to impaired decision-making, without associated rationale of potential future need (Nakaaki *et al.*, [2007a](#)).

We have seen several patients who were ultimately diagnosed with bvFTD after having carried a diagnosis of atypical schizophrenia or a related diagnosis. Overall, schizophrenia and FTD have very different epidemiologic features, particularly average age of onset, and psychotic symptoms such as hallucinations and delusions are rare in FTD (Mendez *et al.*, [2008](#)). However, there is a significant overlap between negative symptoms of schizophrenia and apathy of bvFTD. Negative symptoms are traditionally described with a specific terminology mainly used in the context of psychotic disorders (e.g., avolition, alogia, amotivation), but essentially refer to lack of motivation, initiative, and emotional reactivity, which are core features of apathy (Robert *et al.*, [2009](#)). As such, apathy secondary to FTD and negative symptoms due to schizophrenia may be indistinguishable in themselves. Negative symptoms are common in the prodromal and residual phases of schizophrenia (i.e., when positive symptoms do not dominate), often leading to a progressive withdrawal from social interactions and activities. In addition, there may be overlapping cognitive features. Schizophrenia is associated with mild cognitive deficits in attention, working memory, executive function, declarative memory, and processing speed, which can mimic early deficits of bvFTD (Lewandowski *et al.*, [2011](#)). Disorganized speech and idiosyncratic use of words neologisms could be confused with the lexical and phonologic paraphasias of PPA or some of the clang-association type speech of bvFTD. Interestingly, bvFTD and schizophrenia share common deficits in social cognition (Amodio and Frith, [2006](#)), such as the inability to detect the intent

of other persons (theory of mind). Finally, both disorders are usually associated with limited or absent insight.

Given the overlap in negative and cognitive symptoms, the clinical distinction is made based on the presence of positive psychotic symptoms and the longitudinal history. The classic course of schizophrenia starts with a prodrome between late teens and mid-30s, followed by episodic exacerbations of symptoms, and a variable level of residual deficits. When this longitudinal history with onset prior to 35 is elicited, it is usually sufficient to distinguish it from bvFTD. Differentiating bvFTD from late-onset schizophrenia (i.e., onset after age 40) can be more challenging (Velakoulis *et al.*, [2009](#)).

Social deficits in communication and interpersonal interactions are the core features of autism spectrum disorders (ASD) (American Psychiatric Association, [2013b](#)); given the prominence of social behavioral deficits in bvFTD, it is not surprising that these disorders have been considered to have similar circuit dysfunction. Despite overlap in neuropsychological impairments, differentiating bvFTD from autism spectrum disorder and/or intellectual disability is fairly straightforward since symptoms of the latter two disorders have to be present since early development (American Psychiatric Association, [2013b](#)). When assessing for the first time an adult with impairments suggestive of social cognitive deficits, obtaining a developmental history (including collateral information from family) confirming the appearance of ASD symptoms in childhood and lack of clear progression over time is sufficient to exclude bvFTD. It has been argued that some cases of bvFTD phenocopies (Midorikawa and Kawamura, [2012](#)) could in fact suffer from an undiagnosed mild ASD without accompanying language impairment (previously known as Asperger syndrome) exhibiting increased behavioral disturbance with aging (Hornberger *et al.*, [2008](#);

Midorikawa and Kawamura, [2012](#)). We contend that a diagnosis of ASD should not be made without clear evidence of developmental deficits.

In the early stages of some cases of bvFTD, it can be challenging to ascertain whether distractibility, inattentiveness, and organization deficits could be due to long-standing adult ADHD (diagnosed or undiagnosed) instead of a neurodegenerative process. Although hyperactivity and impulsivity are less common in adult ADHD than inattentiveness (American Psychiatric Association, [2013b](#)), these features also overlap bvFTD (Pose *et al.*, [2013](#)). Restlessness, repetitive movements, and impulsive decision-making can be seen in both conditions. Despite these similarities, there are important phenomenologic distinctions. Repetitive behaviors in bvFTD tend to be stereotyped and perseverative, as opposed to non-specific restlessness and fidgetiness in ADHD. Importantly, adults with ADHD usually have a fair insight about their inattentiveness and/or impulsivity, as opposed to the anosognosia characterizing bvFTD. As with ASD, the key in making this diagnostic distinction is to elicit a history of similar or more severe ADHD symptoms in childhood, starting at least before age 12.

Diagnostic assessment

History of symptoms

It is of vital importance that the history is obtained from a source very familiar with the patient, typically a spouse or other close relative. The history is taken not only with respect to the manifest symptoms, but also in relation to the patient's lifelong temperament, comportment, and habits. Generally the complaint consists of insidious coarsening of conduct and habits; or it is the gradually progressive loss of speech fluency or

comprehension; or it may be worsening self-neglect and abandonment of work, social routines, and relationships ([Figure 8.2](#)).

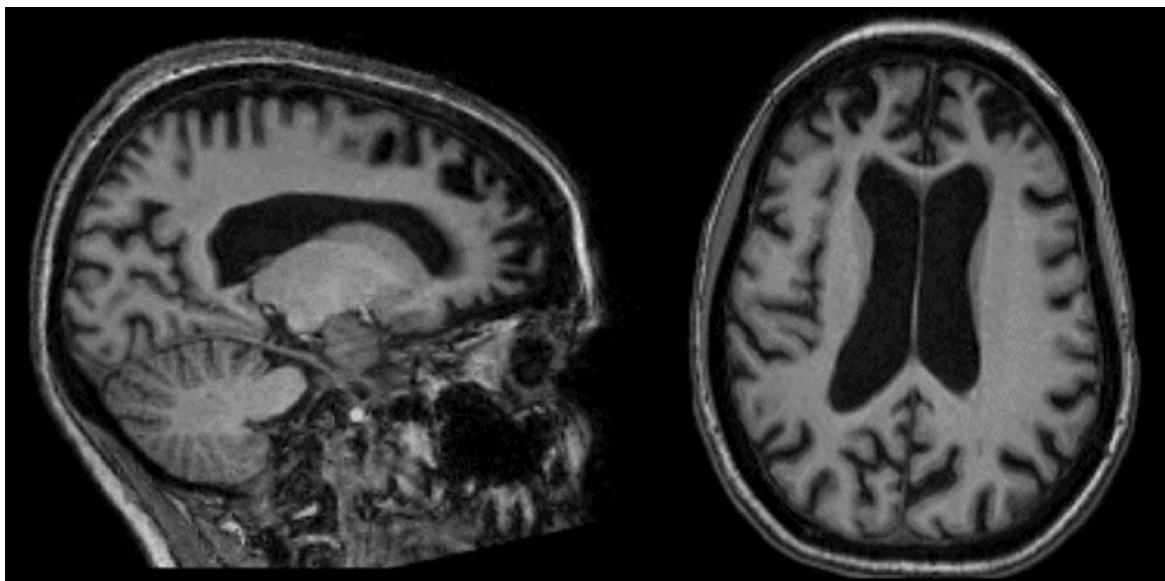


Figure 8.2 This 49-year-old woman developed gradually progressive difficulty performing the duties of her job and her routine home activities with her family (insidious functional impairment). She had apathy and disinhibition, was impulsive, and no longer seemed to express concern as she had previously done for her daughter's problems (lack of empathy). There was no obvious memory loss or spatial disorientation. On examination, she had severe impairments in working memory and executive function (with perseveration and difficulties with phonemic verbal fluency). Brain MRI showed prominent prefrontal atrophy on sagittal (left) and axial (right) T1-weighted images. Diagnosis was probable bvFTD.

It is also crucial to interview the source separately, which, while time-consuming, facilitates disclosure and candor, minimizes recrimination from the patient, and provides a “clean” view of the patient's awareness of the problem. While interviewing the source, the physician might also inquire about that person's experience of the patient's illness (i.e., the costs and stresses, and how these are managed), if the source is also a carer or is living with the patient.

By starting the interview with open-ended questioning, the physician will be able to identify the most distressing aspects of the illness, because patients and families will, given the opportunity, usually begin with the most pressing or painful aspects of the problem. From a diagnostic perspective, it is essential to capture the chronology of symptoms, noting the approximate onset of the illness, and the timing, order, and progression of the symptoms. In bvFTD, changes in conduct, habits, activity, and speech typically precede the development of amnesia, disorientation, or apraxia. The illness may also be associated with falls and parkinsonian symptoms, or with muscle wasting and weakness (which suggests coincident ALS and a more malignant prognosis). The physician should also inquire about prior psychiatric history, and probe for symptoms and chronologic patterns (such as lengthy duration, lack of progression, and discrete episodes interspersed with a normal state) that may point to a primary psychiatric disorder rather than FTD. These include chronic paranoia and delusions, prolonged episodes of anxiety and depression, long-standing aloofness and awkwardness (spanning decades rather than a few years), recurring mania, depression, or distressing compulsions (compulsions in FTLD are generally not accompanied by emotional distress).

The possibility of conditions such as hyperthyroidism should also be explored (by inquiring about, for example, heat intolerance, weight loss despite excessive eating, and palpitations) because features such as irritability, restlessness, increased eating (with decreased satiation), and distractibility may mimic FTLD. Finally, careful documentation of disability is the basis for planning immediate and future care. These include handicaps such as disorientation to situations, impaired communication, failures in self-care and grooming routines, abnormal feeding, and loss of bladder and bowel control.

Structure can be imposed on the history-taking process by using specific FTLD symptom inventories (Bozeat *et al.*, [2000](#); Snowden *et al.*, [2001](#)), the Frontal Behavioral Inventory (Kertesz *et al.*, [1997](#)), or the Neuropsychiatric Inventory (NPI) (Cummings, [1997](#)). Some of these instruments can be given to caregivers in advance as questionnaires, or used to structure an office-based interview. We have developed structured interviews targeting social and language symptoms in FTLD (Sapolsky *et al.*, [2010](#); Bickart *et al.*, [2014](#)), and instruments have also been developed to quantify disability in FTLD (Knopman *et al.*, [2008](#); Mioshi *et al.* [2010](#); Onyike *et al.*, [2011](#)). Further details on assessment instruments for disability and carer burden and distress are reviewed in [Chapter 16](#).

The office-based cognitive examination

In the initial office assessment of a patient with suspected FTLD, a basic cognitive examination is essential. Most commonly used cognitive screening instruments, such as the Mini-Mental State Examination, are insensitive to the cognitive and behavioral deficits of FTLD, as described in detail in [Chapter 9](#). Office-based general cognitive testing instruments thought to be more sensitive to FTLD include the Montreal Cognitive Assessment (MCA) and Addenbrooke's Cognitive Examination (ACE) (Mathuranath *et al.*, [2000](#)). The Frontal Assessment Battery (Dubois *et al.*, [2000](#)) is a brief (~10 minutes) cognitive and psychomotor assessment that has demonstrated sensitivity to FTLD. Although these tests will often identify deficits in patients with FTD, some patients perform normally early in the course of the disease.

Abnormal results on these tests support suspicions of a dementia, and any result will serve as a starting point for evaluating changes with passage of time or in response to a prescription. The clinician will need to spend

additional focused time assessing speech and language in patients with suspected PPA.

The neurologic examination in suspected FTLN syndromes

A neurologic examination is essential, working especially to determine whether there are abnormalities in eye movements or gait, limb or buccofacial apraxia, extrapyramidal signs, primitive reflexes, or evidence of motor neuron disease. Impersistence and distractibility can present challenges during the neurologic exam. Most cases will have a normal physical exam in the early stages, or the exam may show subtle signs suggestive of cerebral dysfunction such as one or more of snout, sucking, rooting, or grasp reflexes.

Neuropsychological testing in FTLN syndromes

Neuropsychological assessment can be invaluable in patients suspected of having FTLN spectrum disorders. Although some patients may perform adequately on brief office-based cognitive testing typically performed by a neurologist, psychiatrist, geriatrician, or other physician, the neuropsychologist may be able to detect abnormalities on extended testing. In at least some very mild cases, however, reasonably extensive neuropsychological assessment can be normal (Gregory *et al.*, [1999](#)). Torralva, Manes, and colleagues have compiled a set of previously developed tests emphasizing “real-life” elements of executive function as well as social cognition (Torralva *et al.*, [2009](#)). This test battery demonstrated higher sensitivity to mild FTD than many standard tests included in typical dementia neuropsychological batteries. Another similar approach was taken by Funkiewiez, Dubois, and colleagues, who assembled the Social cognition and Emotion Assessment (SEA), and ultimately

determined that a subset (facial emotion recognition and faux pas) of the original tests were most sensitive to bvFTD (Funkiewiez *et al.*, [2012](#)), as described in more detail in [Chapter 9](#).

The combination of findings from the assessments described above can be used to determine whether a patient fulfills current diagnostic criteria (Rascovsky *et al.*, [2011](#)) for “possible” bvFTD or one of the progressive aphasias. For bvFTD, the clinician's confidence can be formally elevated to “probable” bvFTD if neuroimaging findings are present as described next. A similar approach is taken by many clinicians in diagnosing PPA, although the criteria do not specify these levels of confidence formally (Gorno-Tempini *et al.*, [2011](#)). Assessment by a speech and language pathologist is invaluable in the evaluation of a patient with speech and/or language symptoms.

Neuroimaging, fluid biomarkers, and other diagnostic tests

Neuroimaging is an important part of the diagnostic workup of FTLD, and has made valuable contributions to our understanding of the specific subtype disorders. Both structural (MRI) and functional (PET, SPECT [single photon emission tomography]) neuroimaging may be valuable for the investigation of anatomical, metabolic, or perfusion abnormalities in FTLD. See [Chapter 10](#) for more details about these techniques and data interpretation.

MRI is critical in the diagnostic workup of suspected FTLD for both the exclusion of other potential causes of slowly progressive frontal lobe syndromes, such as tumors, cerebrovascular disease, or the newly identified “sagging brain syndrome,” and for the identification of abnormalities consistent with FTLD neurodegenerative syndromes. Frontal and/or anterior temporal atrophy is the typical finding, and is often more prominent in the

right hemisphere in bvFTD and the left hemisphere in PPA ([Figure 8.3](#)). Metabolic (FDG-PET) or perfusion (SPECT or arterial spin labeling [ASL] MRI) imaging can be useful in addition to MRI for the identification of abnormalities when anatomical changes are subtle or undetectable. In some cases, both structural and functional neuroimaging may be normal early in the course of what ultimately declares itself over time as FTD (Gregory *et al.*, [1999](#)). Electroencephalography is not commonly recommended in the diagnostic evaluation of suspected FTD, but may demonstrate anterior or focal slowing consistent with frontal neurodegeneration.

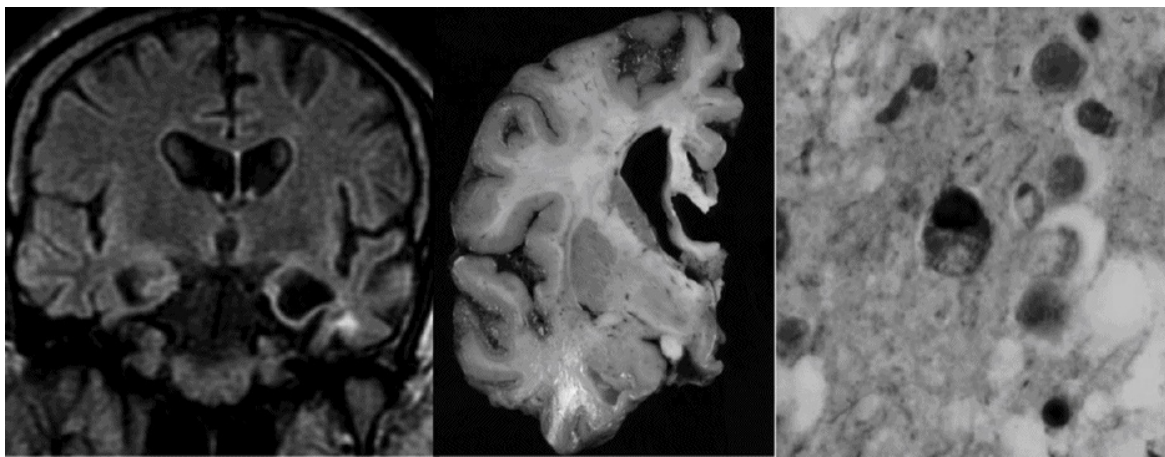


Figure 8.3 This man insidiously developed compulsivity, lack of empathy, impulsivity, and risk-taking behavior at age 27. A coronal FLAIR MRI (left image of panel) demonstrated left greater than right temporal lobe atrophy with hyperintensity suggestive of gliosis. He died at age 33, with post-mortem frontotemporal atrophy with knife-like gyri (middle image of panel) and histologic evidence of neuronal and glial cell loss and gliosis with prominent tauopathy and Pick bodies (right image of panel).

With the advent of neuroimaging tracers that bind to specific pathologic molecules, such as Pittsburgh compound B (PiB) (Klunk *et al.*, [2004](#)) or the growing number of putative tau ligands (Small *et al.*, [2006](#); Fodero-Tavoletti *et al.*, [2011](#); Chien *et al.*, [2013](#); Maruyama *et al.*, [2013](#)), it is possible to investigate clinicopathologic relationships in vivo. Extensive

efforts are underway to develop tracers specific for additional pathologic markers. This will surely lead to a revolution in our understanding of the spectrum of FTD. Additional details on amyloid imaging in FTLD are reviewed in [Chapter 10](#). In the Massachusetts General Hospital FTD Unit, we are actively investigating putative tau PET ligands, with exciting preliminary results ([Figure 8.4](#)).

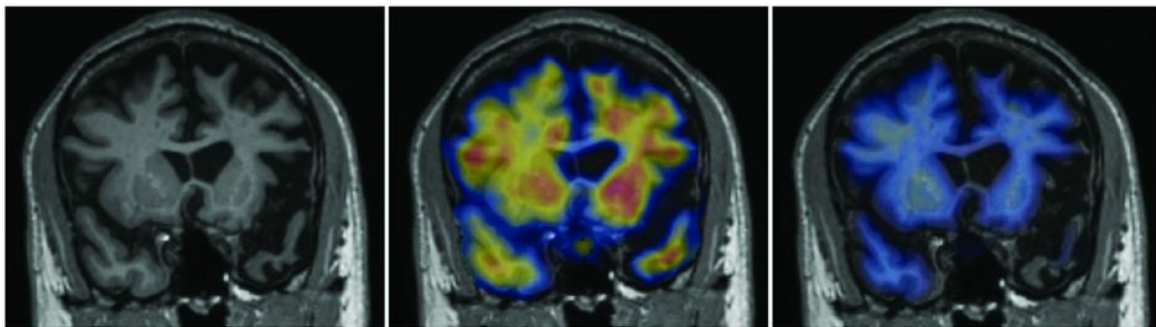


Figure 8.4 Brain scans from a patient with the non-fluent variant of primary progressive aphasia, illustrating left-lateralized frontal, insular, and anterior temporal atrophy in the MRI scan (left image of panel; note that the left side of the brain is shown on the right side of the image). [^{18}F]-T807 tau PET imaging (middle image of panel) shows left-lateralized elevated signal in atrophic frontal, insular, and anterior temporal regions. [^{11}C]-PiB amyloid PET imaging (right image of panel) shows non-specific background signal consistent with an “amyloid-negative” scan. Although validation of [^{18}F]-T807 as an imaging biomarker of FTLD-tau pathology is ongoing, we believe that this type of multimodal imaging will increasingly take on an important role in clinical research, trials, and ultimately practice in determining, for example as shown here, that the patient likely harbors non-amyloid FTLD-tau pathology as the basis of his PPA. Dr. Dickerson thanks colleague Dr. Keith Johnson for his generous collaboration in this project.

CSF biomarkers are being investigated in FTLD (Hu *et al.*, [2011](#)), but are not yet mature enough for use in clinical practice. In some cases, the exclusion of an atypical form of AD can be helpful by analyzing CSF for amyloid- β and tau. General CSF investigation may be valuable to rule out

other neurologic disorders if the patient has atypical features or a more rapid course. [Chapter 11](#) reviews fluid biomarkers for FTLD spectrum disorders in detail.

If clinical evidence of motor neuron disease is present, especially if it is subtle, electromyography can provide valuable information regarding the presence of upper or lower motor neuron dysfunction, which may be critical for prognosis.

Finally, genetic consultation and testing should be considered in cases of suspected FTLD. We employ an approach similar to that described in detail in [Chapter 12](#).

Clinical course of FTD: the value of longitudinal reassessment of diagnostic classification

The early symptoms help determine the major subtypes of FTLD, but as the disease progresses, involvement of other frontotemporal and subcortical brain regions often result in the development of symptoms characteristic of the other subtypes of FTLD (Kertesz *et al.*, 2005, 2007; Seeley *et al.*, [2005](#)). For example, patients with svPPA may develop disinhibition, compulsivity, and other behavioral symptoms, while bvFTD patients may develop speech, language, and/or semantic deficits.

Overall, survival after diagnosis is typically 6 to 10 years, with bvFTD patients having the shortest mean survival at 3.4 years, PPA survival at 4.5 years, and svPPA patients having the longest survival (Grasbeck *et al.*, [2003](#)). A more recent study suggests a slightly better prognosis for bvFTD patients, with a median survival of 4.2 years from diagnosis (Garcin *et al.*, [2009](#)). The development of early motor symptoms or signs is a poor

prognostic feature in all forms of FTD (Hu *et al.*, [2009](#)), as is early language impairment in bvFTD (Garcin *et al.*, [2009](#)). Recent data suggest that SD patients may commonly have a very slow progression, with 50% of patients alive at 12.8 years after diagnosis in a large cohort of 100 patients (Hodges *et al.*, [2010](#)). The ultimate development of markers of the specific form of neuropathology may be important for prognostication, with one autopsy study of 71 patients indicating that tau pathology was associated with shorter (three years) survival than non-tau forms of FTLD pathology (eight years) (Xie *et al.*, [2008](#)).

In our practice, we always discuss the value of autopsy with family members and with patients if possible. Despite continued improvements in the use of clinical and biomarker data for probabilistic prediction of FTLD or non-FTLD pathology, every specialized center continues to observe surprising cases. Not only is this information important for providing family members with the greatest detail possible about the patient's disease, it also contributes in extremely valuable ways to ongoing research efforts.

A recommendation for the diagnostic terminology used in FTLD

After the patient is evaluated, we bring all the information together to formulate our summary by stating that the patient's overall clinical status is consistent with one of the following categories: Cognitively Normal, Mild Cognitive Impairment (DSM-5's Minor Neurocognitive Disorder), or Dementia (DSM-5's Major Neurocognitive Disorder). Once we have established the overall clinical status, we describe the syndrome in greater detail (e.g., svPPA or bvFTD) and whether or not the patient meets full research diagnostic criteria. We also then describe additional clinical

features (e.g., “with behavioral symptoms” or “with extrapyramidal motor signs”), or in some cases whether a secondary diagnosis is present (e.g., “with secondary development of motor neuron disease or progressive supranuclear palsy syndrome”). Finally, we state our suspicion with regard to neuropathology using probabilistic clinicopathologic data and any biomarker or genetic information available.

References

Adams RD (1966) Further observations on normal pressure hydrocephalus. *Proc R Soc Med* **59**:1135–1140.

American Psychiatric Association (2013a) Neurocognitive disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. Arlington VA: American Psychiatric Association.

American Psychiatric Association (2013b) *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. Arlington, VA: American Psychiatric Association.

Ames D, Cummings J, Wirshing W, Quinn B, Mahler M (1994) Repetitive and compulsive behavior in frontal lobe degenerations. *J Neuropsychiatry Clin Neurosci* **6**:100–113.

Amodio DM, Frith CD (2006) Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci* **7**:268–277.

Baborie A, Griffiths TD, Jaros E *et al.* (2012) Frontotemporal dementia in elderly individuals. *Arch Neurol* **69**:1052–1060.

Berrios GE, Girling DM (1994) Introduction: Pick's disease and the ‘frontal lobe’ dementias. *Hist Psychiatry* **5**:539–547.

Bickart KC, Brickhouse M, Negreira A *et al.* (2014) Atrophy in distinct

corticolimbic networks in frontotemporal dementia relates to social impairments measured using the Social Impairment Rating Scale. *J Neurol Neurosurg Psychiatry* **85**:438–448.

Borroni B, Alberici A, Grassi M *et al.* (2010) Is frontotemporal lobar degeneration a rare disorder? Evidence from a preliminary study in Brescia county, Italy. *J Alzheimers Dis* **19**:111–116.

Bozeat S, Gregory CA, Ralph MA, Hodges JR (2000) Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry* **69**:178–186.

Brodtmann A, Cowie T, McLean C, Darby D (2013) Phenocopy or variant: a longitudinal study of very slowly progressive frontotemporal dementia. *BMJ Case Rep* 2013.

Brun A, Englund E, Gustafson L *et al.* (1994) Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry* **57**:416–418.

Cerami C, Marcone A, Galimberti D *et al.* (2011) From genotype to phenotype: two cases of genetic frontotemporal lobar degeneration with premorbid bipolar disorder. *J Alzheimers Dis* **27**:791–797.

Chien DT, Bahri S, Szardenings AK *et al.* (2013) Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J Alzheimers Dis* **34**:457–468.

Constantinidis J, Richard J, Tissot R (1974) Pick's disease. Histological and clinical correlations. *Eur Neurol* **11**(4):208–217.

Cummings JL (1997) The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* **48**:S10–16.

Davies RR, Kipps CM, Mitchell J *et al.* (2006) Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol* **63**:1627–1631.

Dobson-Stone C, Hallupp M, Bartley L *et al.* (2012) *C9ORF72* repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. *Neurology* **79**:995–1001.

Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: a Frontal Assessment Battery at bedside. *Neurology* **55**:1621–1626.

Floris G, Borghero G, Cannas A *et al.* (2013) Bipolar affective disorder preceding frontotemporal dementia in a patient with *C9ORF72* mutation: is there a genetic link between these two disorders? *J Neurol* **260**:1155–1157.

Fodero-Tavoletti MT, Okamura N, Furumoto S *et al.* (2011) 18F-THK523: a novel in vivo tau imaging ligand for Alzheimer's disease. *Brain* **134**:1089–1100.

Funkiewiez A, Bertoux M, de Souza LC, Levy R, Dubois B (2012) The SEA (Social cognition and Emotional Assessment): a clinical neuropsychological tool for early diagnosis of frontal variant of frontotemporal lobar degeneration. *Neuropsychology* **26**:81–90.

Garcin B, Lillo P, Hornberger M *et al.* (2009) Determinants of survival in behavioral variant frontotemporal dementia. *Neurology* **73**:1656–1661.

Gislason TB, Sjogren M, Larsson L, Skoog I (2003) The prevalence of frontal variant frontotemporal dementia and the frontal lobe syndrome in a population based sample of 85 year olds. *J Neurol Neurosurg Psychiatry* **74**:867–871.

Gorno-Tempini ML, Hillis AE, Weintraub S *et al.* (2011) Classification of primary progressive aphasia and its variants. *Neurology* **76**:1006–1014.

Grasbeck A, Englund E, Horstmann V, Passant U, Gustafson L (2003) Predictors of mortality in frontotemporal dementia: a retrospective study of the

prognostic influence of pre-diagnostic features. *Int J Geriatr Psychiatry* **18**:594–601.

Gregory CA, Serra-Mestres J, Hodges JR (1999) Early diagnosis of the frontal variant of frontotemporal dementia: how sensitive are standard neuroimaging and neuropsychologic tests? *Neuropsychiatry Neuropsychol Behav Neurol* **12**:128–135.

Gustafson L (1987) Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. *Arch Gerontol Geriatr* **6**:209–223.

Hodges JR, Mitchell J, Dawson K *et al.* (2010) Semantic dementia: demography, familial factors and survival in a consecutive series of 100 cases. *Brain* **133**:300–306.

Hornberger M, Piguet O, Kipps C, Hodges JR (2008) Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology* **71**:1481–1488.

Hornberger M, Shelley BP, Kipps CM, Piguet O, Hodges JR (2009) Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? *J Neurol Neurosurg Psychiatry* **80**:591–593.

Hornberger M, Piguet O, Graham AJ, Nestor PJ, Hodges JR (2010) How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology* **74**:472–479.

Hornberger M, Wong S, Tan R *et al.* (2012) In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. *Brain* **135**:3015–3025.

Hu WT, Seelaar H, Josephs KA *et al.* (2009) Survival profiles of patients with frontotemporal dementia and motor neuron disease. *Arch Neurol* **66**:1359–1364.

Hu WT, Chen-Plotkin A, Grossman M *et al.* (2011) Novel CSF biomarkers for

frontotemporal lobar degenerations. *Neurology* **75**:2079–2086.

Ibach B, Koch H, Koller M, Wolfersdorf M; Workgroup for Geriatric Psychiatry of the Psychiatric State Hospitals of Germany, Workgroup for Clinical Research of the Psychiatric State Hospitals of Germany (2003) Hospital admission circumstances and prevalence of frontotemporal lobar degeneration: a multicenter psychiatric state hospital study in Germany. *Dement Geriatr Cogn Disord* **16**:253–264.

Kertesz A, Davidson W, Fox H (1997) Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. *Can J Neurol Sci* **24**:29–36.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG (2005) The evolution and pathology of frontotemporal dementia. *Brain* **128**(Pt 9):1996–2005.

Kertesz A, Blair M, McMonagle P, Munoz DG (2007) The diagnosis and course of frontotemporal dementia. *Alzheimer Dis Assoc Disord* **21**(2):155–163.

Kertesz A, Ang LC, Jesso S *et al.* (2013) Psychosis and hallucinations in frontotemporal dementia with the C9ORF72 mutation: a detailed clinical cohort. *Cogn Behav Neurol* **26**:146–154.

Khan BK, Yokoyama JS, Takada LT *et al.* (2012) Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. *J Neurol Neurosurg Psychiatry* **83**:358–364.

Kipps CM, Davies RR, Mitchell J *et al.* (2007) Clinical significance of lobar atrophy in frontotemporal dementia: application of an MRI visual rating scale. *Dement Geriatr Cogn Disord* **23**:334–342.

Klunk WE, Engler H, Nordberg A *et al.* (2004) Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* **55**:306–319.

Knopman DS, Petersen RC, Edland SD, Cha RH, Rocca WA (2004) The

incidence of frontotemporal lobar degeneration in Rochester, Minnesota, 1990 through 1994. *Neurology* **62**:506–508.

Knopman DS, Kramer JH, Boeve BF *et al.* (2008) Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* **131**:2957–2968.

Le Ber I, Camuzat A, Hannequin D *et al.* (2008) Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain* **131**:732–746.

Lewandowski K, Cohen B, Öngür D (2011) Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychol Med* **41**:225.

Mann-Wrobel MC, Carreno JT, Dickinson D (2011) Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. *Bipolar Disord* **13**:334–342.

Maruyama M, Shimada H, Suhara T *et al.* (2013) Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron* **79**:1094–1108.

Masellis M, Momeni P, Meschino W *et al.* (2006) Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. *Brain* **129**:3115–3123.

Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR (2000) A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* **55**:1613–1620.

McGirr A, Mohammed S, Kurlan R, Cusimano MD (2013) Clinical equipoise in idiopathic normal pressure hydrocephalus: a survey of physicians on the need for randomized controlled trials assessing the efficacy of cerebrospinal fluid diversion. *J Neurol Sci* **333**:13–18.

McKhann GM, Albert MS, Grossman M *et al.* (2001) Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* **58**:1803–1809.

Meisler MH, Grant AE, Jones JM *et al.* (2013) C9ORF72 expansion in a family with bipolar disorder. *Bipolar Disord* **15**:326–332.

Mendez MF, Shapira JS (2008) The spectrum of recurrent thoughts and behaviors in frontotemporal dementia. *CNS Spectr* **13**:202–208.

Mendez M, Perryman K, Miller B, Swartz J, Cummings J (1997) Compulsive behaviors as presenting symptoms of frontotemporal dementia *J Geriatr Psychiatry Neurol* **10**:154–157.

Mendez MF, Shapira JS, Miller BL (2005) Stereotypical movements and frontotemporal dementia. *Mov Disord* **20**:742–745.

Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE (2008) Psychotic symptoms in frontotemporal dementia: prevalence and review. *Dement Geriatr Cogn Disord* **25**:206–211.

Mesulam MM (1982) Slowly progressive aphasia without generalized dementia. *Ann Neurol* **11**:592–598.

Midorikawa A, Kawamura M (2012) The relationship between subclinical Asperger's syndrome and frontotemporal lobar degeneration. *Dement Geriatr Cogn Dis Extra* **2**:180–186.

Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR (2010) Clinical staging and disease progression in frontotemporal dementia. *Neurology* **74**:1591–1597.

Modirrousta M, Price BH, Dickerson BC (2013) Neuropsychiatric symptoms in primary progressive aphasia: phenomenology, pathophysiology, and approach to assessment and treatment. *Neurodegener Dis Manag* **3**:133–146.

Nakaaki S, Murata Y, Sato J *et al.* (2007a) Impairment of decision-making cognition in a case of frontotemporal lobar degeneration (FTLD) presenting with pathologic gambling and hoarding as the initial symptoms. *Cogn Behav Neurol* **20**:121–125.

Nakaaki S, Murata Y, Shinagawa Y *et al.* (2007b) A case of late-onset obsessive compulsive disorder developing frontotemporal lobar degeneration. *J Neuropsychiatry Clin Neurosci* **19**(4):487–488.

Neary D, Snowden JS, Northen B, Goulding P (1988) Dementia of frontal lobe type. *J Neurol Neurosurg Psychiatry* **51**:353–361.

Neary D, Snowden JS, Gustafson L *et al.* (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**:1546–1554.

Onyike CU, Sloane KL, Smyth SF *et al.* (2011) Estimating severity of illness and disability in frontotemporal dementia: preliminary analysis of the Dementia Disability Rating (DDR). *Acta Neuropsychol* **9**:141–153.

Onyike CU, Pletnikova O, Sloane KL *et al.* (2013) Hippocampal sclerosis dementia: an amnesic variant of frontotemporal degeneration. *Dement Neuropsychol* **7**:83–87.

Perry RJ, Miller BL (2001) Behavior and treatment in frontotemporal dementia. *Neurology* **56**:S46–S51.

Pompanin S, Perini G, Toffanin T *et al.* (2012) Late-onset OCD as presenting manifestation of semantic dementia. *Gen Hosp Psychiatry* **34**:102.e101–102.e104.

Pose M, Cetkovich M, Gleichgerrcht E *et al.* (2013) The overlap of symptomatic dimensions between frontotemporal dementia and several psychiatric disorders that appear in late adulthood. *Int Rev Psychiatry*

25:159–167.

Rankin KP, Santos-Modesitt W, Kramer JH *et al.* (2008) Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry* **69**:60–73.

Rascovsky K, Hodges JR, Knopman D *et al.* (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**:2456–2477.

Robert P, Onyike C, Leentjens A *et al.* (2009) Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry* **24**:98–104.

Rohrer JD, Geser F, Zhou J *et al.* (2010) TDP-43 subtypes are associated with distinct atrophy patterns in frontotemporal dementia. *Neurology* **75**:2204–2211.

Sapolsky D, Bakkour A, Negreira A *et al.* (2010) Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia. *Neurology* **75**:358–366.

Seeley WW, Bauer AM, Miller BL *et al.* (2005) The natural history of temporal variant frontotemporal dementia. *Neurology* **64**:1384–1390.

Small GW, Kepe V, Ercoli LM *et al.* (2006) PET of brain amyloid and tau in mild cognitive impairment. *N Engl J Med* **355**:2652–2663.

Snowden JS, Goulding PJ, Neary D (1989) Semantic dementia: a form of circumscribed cerebral atrophy. *Behav Neurol* **2**:167–182.

Snowden JS, Bathgate D, Varma A *et al.* (2001) Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* **70**:323–332.

Snowden JS, Neary D, Mann DM (2004) Autopsy proven sporadic

frontotemporal dementia due to microvacuolar-type histology, with onset at 21 years of age. *J Neurol Neurosurg Psychiatry* **75**:1337–1339.

Snowden JS, Rollinson S, Thompson JC *et al.* (2012) Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations. *Brain* **135**:693–708.

Torralva T, Roca M, Gleichgerricht E, Bekinschtein T, Manes F (2009) A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain* **132**:1299–1309.

Velakoulis D, Walterfang M, Mocellin R, Pantelis C, McLean C (2009) Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: clinicopathological series and review of cases. *Br J Psychiatry* **194**:298–305.

Warrington EK (1975) Selective impairment of semantic memory. *Q J Exp Psychol* **27**:635–657.

Whitwell JL, Jack CR, Jr., Baker M *et al.* (2007) Voxel-based morphometry in frontotemporal lobar degeneration with ubiquitin-positive inclusions with and without progranulin mutations. *Arch Neurol* **64**:371–376.

Whitwell JL, Dickson DW, Murray ME *et al.* (2012a) Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. *Lancet Neurol* **11**:868–877.

Whitwell JL, Weigand SD, Boeve BF *et al.* (2012b) Neuroimaging signatures of frontotemporal dementia genetics: *C9ORF72*, tau, progranulin and sporadics. *Brain* **135**:794–806.

Wicklund MR, Mokri B, Drubach DA *et al.* (2011) Frontotemporal brain sagging syndrome: an SIH-like presentation mimicking FTD. *Neurology* **76**:1377–1382.

Woolley J, Wilson M, Hung E *et al.* (2007) Frontotemporal dementia and mania.

Am J Psychiatry **164**:1811–1816.

Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP (2011) The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry* **72**:126–133.

Xie SX, Forman MS, Farmer J *et al.* (2008) Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* **79**:126–129.

Chapter 9

Neuropsychological assessment of frontotemporal dementia



Teresa Torralva, Macarena Martinez Cuitiño, and Facundo Manes

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

A diagnosis of one of the frontotemporal dementias (FTD) requires a careful evaluation of diverse patient characteristics including symptoms in daily life, neuropsychological processes, neurologic and psychiatric function, neuroimaging, and genetics. The complexity of the symptoms observed in this disease damaging the frontal and temporal lobes creates the necessity for a very careful neuropsychological examination.

Until recently, neuropsychological studies of the behavioral variant FTD (bvFTD) have typically focused on functions such as episodic and semantic memory, working memory, and executive functioning, and to a lesser degree functions such as attention and visuospatial ability. More investigations need to be done studying all cognitive functions as well as affective and social function and the subtle changes observed in this group of patients early in the disease.

The aim of the present chapter is to describe a selection of the most utilized tests in each domain that have shown utility for the detection of changes in cognition. The first section will be specifically dedicated to describe the neuropsychology of bvFTD and the second one to the language variants: progressive non-fluent aphasia (PNFA), semantic dementia (SD), and logopenic aphasia (LPA).

Behavioral variant FTD

Screening tests

Formal neuropsychological assessment is very important but is time-consuming, complex, and costly. Therefore brief screening tools, easy to administer, with adequate sensitivity, specificity, and predictive value are of great importance to clinicians. The most utilized screening tests for dementia, specifically for differentiating bvFTD from other dementia types, are the Mini-Mental State Examination (MMSE) [1] and the Addenbrooke's Cognitive Examination (ACE) [2] in its different versions: the Addenbrooke's Cognitive Examination – Revised (ACE-R) [3] and the Addenbrooke's Cognitive Examination-III (ACE-III) [4].

Mini-Mental State Examination (MMSE):

This is the world's most popular and widely used brief cognitive status screening tool for bedside assessment. It is a brief 30-point instrument used to screen for cognitive impairment. It is also used to estimate the severity of cognitive impairment and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. It has limited value for diagnosing bvFTD, lacking both sensitivity and specificity. *Patients with bvFTD score normally*

or with only a mildly low MMSE, despite the presence of other cognitive and behavioral deficits.

Addenbrooke's Cognitive Examination (ACE):

During the 1990s Mathuranah and colleagues developed this screening tool which assesses five cognitive domains: attention, memory, verbal fluency, language, and visuospatial abilities. The “ACE” incorporates the items of the MMSE with the addition of other items and shows superior sensitivity and specificity in the detection of cognitive impairment in the earlier stages of dementia. In order to improve the original version of the ACE a new version of the test was developed in 2006: the ACE-R. Lately, the ACE-III has replaced the previous ACE-R. *The ACE-III cognitive domains correlated significantly with standardized neuropsychological tests used in the assessment of attention, language, verbal memory, and visuospatial function. The ACE-III has showed an excellent ability to discriminate Alzheimer's disease (AD) from FTD and also appeared to be very helpful in the assessment of the MCI (mild cognitive impairment).*

Attention

Distractibility, or impaired ability for focused behavior, has been described in the majority of patients with FTD. As most cognitive tests depend either primarily or peripherally on attentional mechanisms, the influence of deficient attentional processes on test performance can be profound.

The most frequent attentional tests used in patients with bvFTD are: the Digit Span Forward [5], the Stroop Color and Word Test [6], Trail Making Test (A) [7], and the Conners' Continuous Performance Test (CPT) [8].

Digit Span Forward:

Digits are presented orally at a rate of one digit/second and participants are asked to repeat the digits in the same order. Testing begins with two digits and

two trials are presented at each span size to a maximum of nine digits. Testing is terminated when the participant fails both times. *bvFTD patients generally show impairment in this task compared with normal controls, making specifically more sequential errors than AD patients* [9, 10].

Stroop Color and Word Test:

This test measures attention, mental speed, mental flexibility, set-shifting, and susceptibility to interference. The patient is asked to read a list of color words printed in black ink, followed by Xs printed in color, and finally words from the first page printed in colors of the second page. *This attention and executive function test has shown to be affected in both AD and bvFTD in the same way, with a slowing down in the naming and interference conditions* [11].

Trail Making Test (A):

This test is considered a test of visual motor tracking, sustained attention, cognitive flexibility, and ability to shift sets. In Test A the individual is asked to draw a line connecting a series of numbered circles in the correct order as quickly as possible. *Although this test of attention is frequently affected in the bvFTD group, especially in moderate and severe stages of the disease, it is not always sensitive enough to the subtle changes in early bvFTD* [9]. Part B of the Trail Making Test is described below under Executive functions.

Conners' Continuous Performance Test (CPT):

This is a computerized assessment of attention, vigilance, and impulsivity. It requires the subject to press a key for any letter except the target letter, with differing inter-stimulus intervals. After the test is completed, the computer program generates a report that includes the number correct, omission errors, commission errors, and various reaction times. *Patients with bvFTD generally show impairment in this task compared with normal controls, showing reduced accuracy over the course of the test and with slower speed of presentation* [10].

Memory

One of the most consistent findings in patients with bvFTD is the relative preservation of episodic memory [12]. Despite the fact that “severe amnesia” is currently an exclusion criterion for bvFTD, memory symptoms are very frequently reported in the initial stages of the disease [13]. Surprisingly few detailed studies have investigated episodic memory in patients with bvFTD, showing inconsistent results [14]. Such inconsistencies could be explained in part by recent studies, which have shown that clinically diagnosed patients with bvFTD vary in their prognosis; some show rapid progressions while others show little or no progression over a decade. They classified these patients with bvFTD into progressive versus phenocopy cases based on their long-term outcome.

Other groups such as Glosser *et al.* [15] also found that bvFTD patients obtained higher free recall, cued recall, and recognition scores than AD patients. They also reported that serial-order recall was more common in bvFTD, suggesting less efficient learning strategies. Kramer *et al.* found that their AD and SD groups were significantly impaired relative to bvFTD on verbal memory, whereas only the AD group was impaired on visual memory [16], suggesting that measuring memory in both verbal and spatial modalities is valuable. Therefore, the exhaustive assessment of the episodic memory domain in bvFTD patients is important to understand deeply the cognitive profile of this group of patients.

Semantic memory also seems to be intact in bvFTD patients, in contrast with both SD and AD patients [17]. Rascovsky *et al.* compared FTD and AD patients with phonemic and semantic category fluency tasks, showing a disparity between letter and semantic category fluency (the semantic index) between the groups [18]. bvFTD patients also perform

better than SD patients on semantic memory tasks such as autobiographical memory and naming [19]. Other types of memory, such as temporal memory, spatial source memory, and prospective memory, should be assessed too when time permits.

The most frequent tests used to assess memory skills in patients with bvFTD are: the Auditory-Verbal Learning Test (AVLT) [20] or a similar word list learning test, the computerized Paired Associate Learning Test (PAL) [21], the Free and Cued Selective Reminding Test (FCSRT) [22], autobiographical memory tests [23], and the Cambridge Behavioural Prospective Memory Test [24].

Auditory-Verbal Learning Test (AVLT):

This easily administered test measures immediate memory span, provides a learning curve, reveals learning strategies – or their absence, elicits retroactive and proactive interference tendencies and tendencies to confusion or confabulation on memory tasks, measures both short-term and longer-term retention, and allows for a comparison between retrieval efficiency and learning. It consists of five presentations with recall of a 15-word list, one presentation of a second 15-word list, and a sixth recall trial, which all together take 10 to 15 minutes. A 30-minute delayed recall trial gives information on how well the patient recalls what was once learned. A recognition trial should be given whenever a patient's delayed recall is less than 13 words, measuring the efficiency of retrieval in patients who demonstrate adequate learning. *While the impact of episodic memory among bvFTD is not without controversy, studies by our group looking at memory measures in bvFTD patients with frontal atrophy have revealed that memory is spared in the earlier stages, but impairments tend to emerge as the disease progresses, likely due to the involvement of executive functions which have an impact on memory acquisition and recall [9]. Perri and collaborators [25] have demonstrated recently that bvFTD patients have differential scores between word-list and*

prose tests, having a superior performance in the latter, reflecting a frontal memory problem as opposed to the AD “mesio-temporal” memory profile.

The computerized Paired Associate Learning Test (PAL)

from the CANTAB (Cambridge Neuropsychological Test Automated Battery) is a test in which subjects are required to learn the association between colored patterns and spatial locations. Boxes are displayed on the screen and are opened in a randomized order where one or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time, and the participant must touch the box where the pattern was originally located. *This test has been shown to be exquisitely sensitive to early AD [21]. By contrast, patients with bvFTD (and SD) generally perform within the normal range at least in the earlier stages of the diseases [26].*

Free and Cued Selective Reminding Test (FCSRT):

The FCSRT is based on a semantic relationship between the presented items and their categories (e.g., what is the name of the fruit?), which allows controlling for an initial and effective registration of the list of words, and secondarily to facilitate the retrieval from stored information. *In the study by Sarazin and colleagues, memory scores could not differentiate bvFTD from AD patients (sensitivity and specificity < 50%) [27]; half of bvFTD patients exhibited a deficit of free recall, total (free + cued) recall, and delayed recall as severe as that of AD patients. The other half had subnormal scores similar to phenocopies and a delayed recall score similar to control subjects.*

Autobiographical memory tests:

These tests typically comprise a free recall procedure, which allows participants to generate events across different life periods, followed, in some instances, by a cued recall procedure to probe further for contextual-rich event information. The Autobiographical Memory Interview (AMI) provides a useful research tool for investigating retrograde amnesia. Patients who may be very similar on standard memory tests can differ markedly in their

autobiographical memory performance. The test assesses a subject's recall of facts from their own past life and also assesses a subject's recall of specific incidents in their earlier life. Both types of memory are assessed across three broad time bands: childhood, early adult life, and recent facts/incidents. It thus allows a measurement of the pattern of autobiographical memory deficit, and the detection of any temporal gradient in retrograde amnesia. *On a test of autobiographical memory, patients in the early stages of Alzheimer's disease typically present a pattern of impairment in memories for their recent life events but a relative preservation in autobiographical memories for earlier phases of their lives [28]; on the contrary, SD patients show more difficulties for remote events. In the study by Thomas-Antérion and colleagues [29], a differential pattern of remote memory deficit for bvFTD patients was observed: patients appeared to have lost access to memories due to executive difficulties.*

Cambridge Prospective Memory Test:

This test assesses difficulties in prospective memory. It is an objective and standardized clinical instrument offering information about a patient's prospective memory or his/her ability to remember to do things at a particular time or within a given interval of time. The shortened version takes 20 minutes and comprises three time-based (T-B) and three event-based (E-B) prospective memory items. *In a recent study [30], SD patients exhibited preserved T-B prospective memory in the context of an impaired E-B prospective memory, contrasting with bvFTD and AD patients who demonstrated global PM impairments.*

Visuospatial function

A few studies have compared visuospatial performance between FTD and AD patients; yet consistent conclusions were not found. Some of them found similar impairments in both groups of patients [31] while others did not.

Therefore, it is not completely clear yet what to expect of a FTD patient when a visuospatial task is assessed. However, AD and bvFTD patients usually fail in visuospatial tests as a consequence of different anatomical substrates and distinctive cognitive mechanisms [32]. Consequently, what we do know is that FTD patients' performance in visuospatial tasks may usually be impaired by their executive difficulties. Executive errors (perseverative) are expected to appear and poor organizational strategies may impair scores on some complex tasks such as copy of the Rey Figure.

The most frequent visuospatial tests used to assess these skills in patients with bvFTD are: the copy of Rey–Osterrieth complex figure [33], the Visual Object and Space Perception Test (VOSP) [34], the Graded Faces Test (GFT) [35], and the Face–Place Test [35]; among others.

The Complex Rey Figure Test (*Drawing*):

This test investigates perceptual organization, visual memory, and strategy.

The subject is asked to copy the figure while the examiner watches the subject's performance closely, and each time the subject completes a section of the drawing the examiner provides a different colored pencil and notes the order of the colors. This method of tracking the performance allows the identification of the execution strategies, according to the original analysis. In addition to the usual scoring method, Osterrieth analyzed the drawings in terms of the patient's strategy as well as specific copying errors. *The seven different procedural types identified by the author are specifically useful in bvFTD patients for understanding the impact of lack of strategy over their performance. In a study conducted by Possin et al. [32], using a simplified version of this figure, it was found that both AD and bvFTD patients failed in tests of figure copy but the association with cerebral areas was differential: the bvFTD performance was associated with smaller right dorsolateral prefrontal cortex volumes and the AD group with right parietal volumes.*

Visual Object and Space Perception Test (VOSP):

This is a nine-test battery that includes cutoff scores for each test. Therefore, these tests can be used individually or the battery can be given as a whole. The first test, *Shape Detection Screening*, checks whether the patient's vision is sufficiently intact to permit further examination. The next four tests are Object Perception Tests, which present views of letters, animals, or objects incomplete or rotated: Incomplete Letters, Silhouettes, Object Decision, and Progressive Silhouettes. The last four tests are Space Perception Tests, Dot Counting, Position Discrimination, and Number Location. *The VOSP battery appears to be effective at assessing visuospatial function and sensitive at detecting visuospatial deficits with almost no demand on executive functions. This test should theoretically be more impaired in AD patients than in bvFTD patients, but has not yet been investigated systematically.*

The Graded Faces Test (GFT):

This is a test of naming and knowledge of famous people comprising items of graded difficulty. The stimuli consist of 30 faces, half of which are of recently famous individuals and half non-recent celebrities. Famous people are drawn from many categories including politicians, statesmen, and personalities from the worlds of acting, music, or sport. *In the study by Clague and colleagues [35], a mild naming deficit was revealed in the bvFTD group.*

The Face–Place Test:

This is a newly developed task that combines naming of famous faces, item recognition, and spatial location [35]. It consists of 40 cards with a photograph of a face on each. Half of these items are shown in a study phase. Afterwards, these cards are repeated but mixed with another half of new famous faces. In this stage, patients should recognize whether they had seen the picture on the card or not. Once recognition has been tested, the subject is asked (for all previously presented faces) in which position the photograph had been seen at study. Administration of the whole test takes approximately

15 minutes. *Clague et al. suggested that patients with fvFTD do not show substantial deficits in the item recognition and spatial components [35].*

Executive functions

Given that the prefrontal cortex is an early site of neuropathology in many cases of FTD, it is to be expected that executive dysfunction would be a major component of the clinical presentation of the disease. The executive dysfunction presented by patients with bvFTD would be characterized by a full range of deficits in multiple domains (e.g., [36]) such as planning (e.g., Tower of London), judgment, reasoning, problem-solving (e.g., Iowa Gambling Task), organization (e.g., Hotel Task, Multiple Errands Test Hospital Version [MET-HV]), attention (e.g., Trail Making Test), abstraction (e.g., Proverbs), mental flexibility (e.g., Wisconsin Card Sorting Test [WCST]), working memory (e.g., Letters and Numbers; backward digit span), inhibitory control (e.g., Stroop Test; Hayling Test) and generative behaviors (e.g., verbal fluency). However, patients with AD [36] and psychiatric patients without an underlying diagnosis of dementia [37] may also present with executive deficits. Nevertheless, the differences in executive abilities may be evident in qualitative aspects of performance and in the types of errors that can occur rather than the overall quantitative scores.

Frontal screening tools

Frontal Assessment Battery (FAB) [38]:

The FAB consists of six subtests, which assess conceptualization, conflicting instructions, motor programming, sensitivity to interference, motor inhibitory control, and prehension behavior. Each subtest is scored on a maximum of 3

points, rendering a total maximum score of 18. Although the authors of the FAB suggested no cutoff score, the original publication had reported a discriminant validity of 89.1% using the total score.

The INECO Frontal Screening (IFS) [39]:

The IFS included three subtests from the FAB (motor programming, conflicting instructions, and motor inhibitory control) and added new subtests that have been shown to be sensitive to executive dysfunction: numerical working memory, verbal working memory, spatial working memory, abstraction capacity, and verbal inhibitory control. The IFS has a maximum possible total score of 30 points. The test takes less than 10 minutes to be administered and scored. A 25-point cutoff score has shown a sensitivity of 96.2% and a specificity of 91.5% in detecting patients with dementia. The IFS total discriminated controls from demented patients, and bvFTD from AD. *As the authors showed (Figure 9.1) the IFS is a brief, sensitive, and specific tool for the detection of executive dysfunction associated with neurodegenerative diseases and could be especially helpful in the differential diagnosis of bvFTD and AD.*

Subtests grouped into the different executive functions tapped by the IFS

Executive function	IFS subtest
Response inhibition and set-shifting	<i>Motor programming</i>
	<i>Conflicting instructions</i>
	<i>Go-No go</i>
	<i>Verbal inhibitory control (Modified Hayling Test)</i>
Abstraction	<i>Proverb interpretation</i>
Working Memory	<i>Backward digit span</i>
	<i>Verbal working memory*</i>
	<i>Spatial working memory**</i>
Central Executive	

Note. IFS = INECO Frontal Screening

*Predominantly verbal (Phonological loop).

**Predominantly visual (visuo spatial sketchpad).

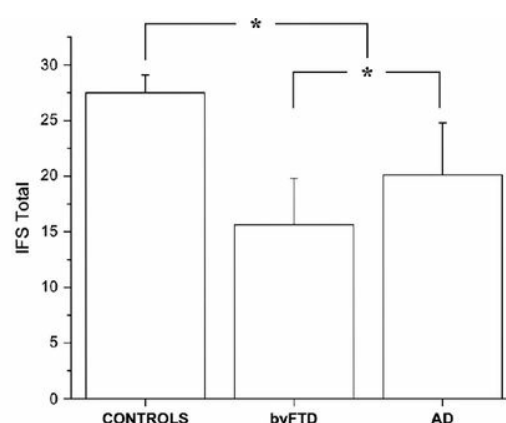


Figure 9.1 The INECO Frontal Screening (IFS) [39].

Classical executive function tests

The most frequent classical executive function tests used in patients with bvFTD are: the backward digit span [5], Letters and Numbers [5], word fluency tests; design fluency tests [40], Trail Making Test Part B [7], Wisconsin Card Sorting Test [41], Tower Tests [42], Hayling Test [43], D-KEFS (The Delis–Kaplan Executive Function System) [44], among others.

Backward digit span:

Participants are presented with sequences ranging from two to eight digits in length and are asked to repeat the digits in the reverse order. This task assesses mental manipulation and working memory. *It is expected that bvFTD patients exhibit deficits in these types of tasks especially in mild and moderate stages of the disease.*

Letters and Numbers:

Participants are presented with an increasing number of letters and digits and are asked to repeat them in a way such that numbers are ordered in an ascending fashion and letters arranged alphabetically. This test also assesses mental manipulation. *Studies by our group looking at executive measures in bvFTD patients showed that early high functioning bvFTD patients had significantly lower scores than normal controls in this test [9].*

Word fluency tests:

The purpose of these tests is to assess spontaneous production of words beginning with a given letter or of a given semantic class in a limited amount of time. For letter fluency (phonetic association), participants were asked to verbally produce as many words as possible beginning with a given letter for 60 seconds (“F”, “A,” or “S”). For category (semantic association) fluency, participants were asked to produce as many animal nouns as possible within the same time frame. *Performance on verbal fluency tasks is one of the most frequently noted means of discriminating between AD and FTD clinically, and even among FTD subtypes [45]. FTD patients tend to generate less*

words beginning with a specific letter in comparison to the total of words generated with a given semantic category (animals). Also, FTD patients in general (and bvFTD patients in particular) showed more generation of “bad words” during letter fluency testing [46] and have more trouble in action fluency [47] in comparison to AD patients.

Trail Making Test Part B:

Participants were asked to join 25 randomly arranged numbers and letters in an alternating fashion. These tests are designed to assess speed of attention, sequencing, mental flexibility, visual search, and set-shifting. *Patients with bvFTD have shown a faster performance on this test than patients with AD or SD, but with a greater number of errors [48]. Studies have also shown that patients whose symptoms have progressed over time (bvFTD), in comparison with those whose clinical symptoms remained stable (phenocopy group), exhibit more deficits on this test [49].*

Wisconsin Card Sorting Test:

This test evaluates the ability to shift from one cognitive set to another. In this test, the subject has to sort cards containing geometric forms which differ in color, shape, and number. The participant's first sorting choice becomes the correct feature, and once a criterion of six consecutive correct sorts is achieved, the subject is told that the rules have changed, and cards must be sorted according to a new feature. After all three features have been used as sorting criteria; subjects must cycle through them again in the same order as they did before. Each time the feature is changed, the next must be discovered by trial and error. *Patients with bvFTD present more impairment in the ability to shift from one cognitive set to another, especially making more perseverative errors [9].*

Tower of London Test:

This is a neuropsychological measure of executive planning and problem-solving based on the original Tower of London (TOL) [50]. The TOL

measures executive planning that involves the ability to conceptualize change, respond objectively, generate and select alternatives, and sustain attention.

Previous studies have found that patients with bvFTD require greater numbers of moves, make more rule violations, and take more time to completion than AD patients [45].

Hayling and Brixton Test:

This test evaluates inhibition of a prepotent response by employing a sentence completion task, with two sections including 15 sentences each. In the first section, subjects are required to complete a sentence with a word that gives a meaningful sense to the sentence. In the second section, the participant completes a sentence with a word that is unconnected to the sentence, which requires inhibiting an automatic response. Errors are recorded for words that do not follow these rules and the time taken to respond. *Patients with bvFTD have shown more inhibitory errors on sentence completion, making this test one of the most sensitive ones to discriminate between bvFTD and AD [14]. Previous studies have also shown that patients whose symptoms have progressed over time (bvFTD), in comparison with those whose clinical symptoms remained stable (phenocopy group), have more deficits on this particular test [49].*

D-KEFS (The Delis–Kaplan Executive Function System):

This is a battery of nine standardized executive function tests (Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, Sorting, Twenty Questions, Word Context, Tower, and Proverb Interpretation) designed to comprehensively assess higher cognitive functions. *Many studies have proven this battery useful in detecting executive dysfunction in patients with FTD, and in distinguishing them from other types of dementias [36]. Possin and colleagues showed that patients with bvFTD made significantly more design repetitions than other dementia groups [51].*

Social cognition tests

Theory of mind tests

Theory of mind (ToM) refers to the capacity to infer others' emotions and mental states. Deficits in ToM are widely regarded as one of the key defining features of bvFTD [9, 52, 53]. The ToM difficulties in bvFTD are significantly larger than the ToM difficulties reported in people with AD [53]. These point to the importance of using a ToM test during the diagnostic process of bvFTD in the early phases of this type of dementia.

The most frequent tests used to assess ToM ability in patients with bvFTD are: the Faux Pas Test [54], the Mind in the Eyes Test [55], Mind in the Voice (e.g., [56]), Face task [57], and first- and second-order false belief tasks [58].

Faux Pas Test of Cognitive and Affective ToM:

In this test the subject is read a story that may or may not contain a social faux pas. In 10 of the stories, there is a faux pas, involving one person unintentionally saying something hurtful or insulting to another. Performance is scored regarding the adequate identification of the faux pas (hits) and the adequate rejection of those stories which did not contain a faux pas (rejects). After recognizing the faux pas, the subject is asked both intentionality and an emotion attribution question, which assess cognitive and affective ToM, respectively. *Recent studies [9, 39, 53] reported ToM impairment in bvFTD patients using these tasks (Figure 9.2).*

Mind in the Eyes Test:

This test consists of 36 photographs showing only the eyes of different actors/actresses portraying different complex mental states. For each set of eyes, the subject is asked to choose one out of four words that best describes what the person on the picture was thinking or feeling. As a control, the subject is asked to judge the gender of each person in each photograph. The

maximum obtainable score is 36. *Multiple studies [9, 39, 53, 59] have reported ToM impairments in bvFTD patients using this test (Figure 9.2).*

Mind in the Voice:

The final version of this test includes 25 items, which consist of neutral content sentences recorded with a particular intonation referring to a particular emotion. The subject must hear every item and then choose from the four answer choices. For example, for the verbalization “Yeah, well, I know nothing about that,” in the original task, the four answers were “Defensive” (correct), “Joking” (incorrect), “Unconcerned,” and “Indignant” (e.g., [58]). *Although no studies have been reported using this test in bvFTD patients, its utilization could be interesting for detecting deficits in this domain.*

Face task:

This task consists of 20 photographs of the same actress, who portrayed different complex mental states. For each set of faces, participants are asked to choose one out of two words best characterizing the feeling or thoughts expressed by the face. Correct answers are rated one, incorrect answers are rated zero. The maximum score of the test is 20. *Although no studies have been reported using this test in bvFTD patients, its utilization could be interesting for detecting deficits in this domain.*

First- and second-order false belief tasks:

The first-order false belief tasks were designed to test subjects’ ability to infer that someone can have a mistaken belief that is different from their own true belief (of the form “A thinks X”). The second-order false belief tasks were used to test the ability to understand what someone else thinks about what another person thinks (of the form “A thinks B thinks X”). Four types of questions are asked per story (false belief, inference, fact, and memory) in an order from least to most explicit, to prevent cueing. *Recent studies (e.g., [59]) have reported impairment in ToM in bvFTD patients using this task. The only exception is the study from Fernandez-Duque and colleagues [60], in*

which the authors found a preserved performance in first-order false belief tasks.

Theory of mind cartoons:

Two sets of cartoon jokes are used – one set (physical) can be understood in physical terms, while the jokes in the other set (ToM) require the participants to perceive the mental state of the main character. The two sets are intermixed in a randomized order and given in a single test session. Participants are required to explain the jokes using the question “Why might someone find this funny?” In explaining the ToM jokes, patients have to use language to indicate that they have correctly perceived the mental state inferred in the cartoon for the interpretation of the joke to be accepted as correct. Each set is scored from a total of 10 with 1 point awarded for each acceptable explanation. *Several studies (e.g., [61]) reported impairment in ToM in bvFTD patients using this task.*

Theory of mind stories:

The task consisted of participants reading 16 stories describing naturalistic social situations and being asked why the characters behaved as they did [62]. Half of the stories required ToM accounts to give a correct explanation, while the other eight required specifically a physical explanation. Each set of eight was scored with one point awarded for each acceptable explanation. *Various studies (e.g., [61]) reported impairment in ToM in bvFTD patients using this task.*

Other tests that are frequently used together with the ToM tests are those utilized to examine the ability to recognize emotions, such as the Awareness of Social Inference Test – Revised (TASIT-R) [63], the Emotional Morphing Test [64, 65], and the Interpersonal Reactivity Index (IRI) questionnaire [66], among others.

The Awareness of Social Inference Test – Revised (TASIT-R):

This is a sensitive test of social perception comprising videotaped vignettes of everyday social interactions. This task introduces contextual cues (e.g., prosody, facial movement, and gestures) and additional processing demands (e.g., adequate speed of information processing, selective attention, and social reasoning) which are absent when viewing static displays. The brief version comprises a series of 20 short (15–60 seconds) videotaped vignettes of trained professional actors interacting in everyday situations. All scripts are neutral in content and do not lend themselves to any particular emotion. After viewing each scene, the test participant is instructed to choose from a forced-choice list the emotion expressed by the focused actor (fearful, surprised, sad, angry, and disgusted). *Savage et al. [67], Rankin et al. [68] and Kipps et al. [69] reported impairment in emotional recognition in bvFTD patients using this task.*

Emotional Morphing Test:

This is a facial expression recognition task featuring six basic emotions (happiness, surprise, sadness, fear, anger, and disgust) taken from a pictures-of-affect series [64]. The pictures have been morphed for each prototype emotion and for a neutral state [65]. Facial morphing is generated by taking a variable percentage of the shape and texture differences between the two standard images: 0% (neutral) and 100% (full emotion). Participants are asked to respond as soon as they recognize the facial expression, and then to identify the facial expression from a forced-choice list of six options. This task measures the accuracy of emotion recognition and reaction times (RTs). *Emotion recognition deficits in bvFTD and SD are known to be amodal, with patients demonstrating impaired recognition of verbal and non-verbal stimuli more consistently demonstrated in negative emotions [70]. Diehl-Schmid and colleagues investigated whether the Ekman 60 Faces Test was capable of differentiating between patients with mild FTD and healthy*

subjects, concluding that it can discriminate between them with 97% diagnostic accuracy (sensitivity: 94%; specificity: 100%) [71].

Interpersonal Reactivity Index (IRI):

This is a standardized, 28-item questionnaire of empathy that yields a total score, as well as 4 subscale scores (perspective-taking, fantasy, empathic concern, and personal distress). Contrasting the perspective-taking and empathic concern subscales can help comparing cognitive and emotional aspects of empathy. Following the procedure of Perry *et al.* [72], two versions of the IRI can be administered – one to the caregiver and one to the patient with bvFTD – and by this method any perceived change over time in the patient's empathy could be quantified, and the patient's insight into the changes perceived by the caregiver can be rated. *Various studies (e.g., [4, 73]) have reported impairment in empathy measures in bvFTD patients using this task.*

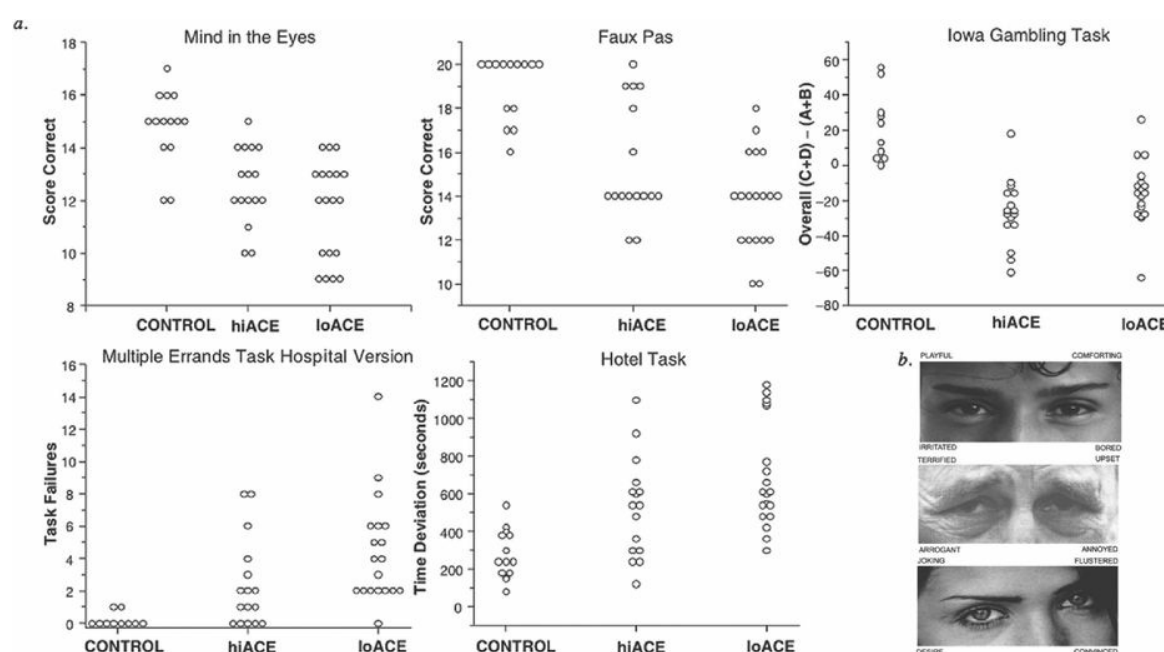


Figure 9.2 Individual patient scores on the tasks of the Executive and Social Cognition Battery (ESCB) [9].

More complex ecologically valid executive function tests

There is a group of tests that it is important to include in order to capture the sometimes-subtle deficits that bvFTD patients present in the early stages of the disease. Some of them are the MET-HV [74], the Hotel Task [75], and the Iowa Gambling Task [76].

Multiple Errands Test Hospital Version (MET-HV):

This test, which is frequently administered at the hospital and its surroundings, requires participants to carry out a number of tasks simulating “real-life” situations where minor inconveniences can take place. While still inside the hospital, the patient is given a card with 4 sets of simple tasks totaling 12 subtasks. Nine rules are clearly stated in the instruction sheet. Errors in this test are categorized as: (1) inefficiencies; (2) rule breaks; (3) interpretation failure; (4) task failures; and (5) total failures. *In our study [10] (Figure 9.2) bvFTD patients made more errors than healthy controls (inefficiencies), acting more impulsively (rule breaks), with no apparent planning, and poor organization of the tasks (task failures).*

The Hotel Task:

This multitasking task comprises five activities that would plausibly need to be completed in the course of running a hotel. The main goal is to attempt to do each of the 5 tasks in 15 minutes. The materials needed to perform these activities are arranged on a desk and randomly distributed between participants and sessions. The details for each of the following tasks are clearly described. *In our study [9] (Figure 9.2) bvFTD patients differed significantly from healthy controls in the optimal time deviation of the task, which is a measure closely associated with planning and flexibility (two of the hallmarks of executive functioning).*

Iowa Gambling Task (IGT):

This is one of the most frequently used decision-making tests in patients with bvFTD. The computerized version of the IGT mimics real-life personal

decision-making activities in real time. Participants are asked to continuously select cards from four decks (A, B, C, and D) in order to make as much money as possible in the game. The task is completed after 100 selections. Following card selection, participants receive a certain amount of reward, but some choices also result in loss of money (penalties). Decks A and B are ultimately risky (large rewards and large punishments) while C and D are more conservative (small rewards and small penalties). In [Table 9.1](#) a summary of studies of decision-making cognition in FTD from the Gleichgerrcht et al. 2010 paper is presented [\[73\]](#), suggesting that the IGT could be used to provide complementary information to a frontal test battery, especially in the early stages of the disease before severe dementia develops.

Table 9.1 Studies of decision-making cognition in FTD [\[73\]](#)

Study	Participants	Decision-making paradigm	Correlation with EF	Other multivariate comparison?	Brain and peripheral biomarkers
Rahman <i>et al.</i> (1999)	8 FTD, 8 controls	CGT	No	No	No
Rahman <i>et al.</i> (2005)	8 FTD	CGT	No	No	Yes: cardiovascular
Torralva <i>et al.</i>	20 FTD, 10 controls	IGT	No	Yes: no correlations	No

(2007)

Torralva <i>et al.</i> (2009)	35 FTD, 14 controls	IGT	Yes: impaired mental flexibility on WCST	Yes: no correlations	No
Manes <i>et al.</i> (2010)	FTD (1)	IGT	No	No	No

Abbreviations: CGT, Cambridge Gambling Task; EF, executive functions; FTD frontotemporal dementia; IGT, Iowa Gambling Task; ToM, theory of mind; WCST, Wisconsin Card Sorting Test.

Some new batteries have emerged, combining different tests, that have proven to be sensitive to early changes in bvFTD patients. Because of space constraints, only two of them will be detailed here: the SEA (Social cognition and Emotional Assessment) [77] and the Executive and Social Cognition Battery (ESCB) [9].

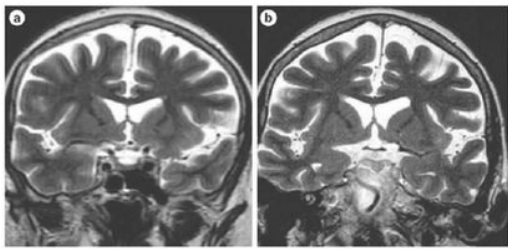
The SEA (Social cognition and Emotional Assessment):

The SEA is an easy tool that has been recently proposed to diagnose and assess emotional recognition and ToM deficits in bvFTD. It consists of five subtests: (1) a facial emotion recognition test (from Ekman pictures), (2) a shortened version of the Faux Pas recognition test evaluating theory of mind, (3) a behavioral control test in which patients must learn to apply a strategy of choice and to modify their choice based on monetary reward, (4) a reversal learning and extinction test where patients must reverse a pattern of reinforced choice after contingencies are unexpectedly reversed, and (5) an apathy scale. *A study conducted by Bertoux and his collaborators demonstrated that both*

the SEA and mini-SEA (a shortened version) scores distinguished early bvFTD from depression with sensitivity and specificity rates above 94% [78]. Unlike standard executive neuropsychological tests, the SEA and the mini-SEA are capable of differentiating depression from bvFTD in the early stages of the disease.

Executive and Social Cognition Battery (ESCB):

This new proposed battery consists of a group of tests that measure performance of “daily life” activities within a “real-life” environment: the Multiple Errands Test; the Hotel Task; complex decision-making (Iowa Gambling Task); and social cognition (ToM tests). *We demonstrated that bvFTD patients with an apparent high performance on a standard neuropsychological test do not differ significantly from controls in their performance on basic cognitive domains or classical tests of executive function, but fail in this battery [9]. Our results suggest that this battery is more sensitive in detecting executive and social cognitive impairment deficits in early bvFTD dementia than classical cognitive measures (see case presentation in [Figure 9.3](#)).*



a | MRI scan of the case patient taken on initial presentation; frontal atrophy.
b | MRI scan taken 2 years after initial presentation showing more-severe frontal atrophy.

Neuropsychological profile of a patient M.C in early stages of bvFTD with normal performance in classical executive tests but impairment in more ecological social executive tests.

Neuropsychological tests	Patient	Controls (n=14)
Addenbrooke's Cognitive Examination	94	94.8 (5.8)
Mini Mental State Examination	30	29.5 (0.8)
Frontal Assessment Battery at bedside	16	17.7 (0.5)
Rey Auditory-Verbal Learning test		
Immediate recall	44	47.1 (7.4)
Delayed recall	4	8.1 (2.5)
Recognition	12	14.3 (0.9)
Logical memory		
Immediate recall	19	24.5 (4.6)
Delayed recall	14	19.2 (5.3)
Digit span forward	7	7.1 (0.9)
Digit span backward	5	4.8 (1.0)
Trail Making Test A	55 s	39.7 s (15.6 s)
Trail Making Test B	74 s	97.7 s (9.8 s)
Boston Naming Test	18	19.8 (0.4)
Phonological verbal fluency	14	15.9 (4.5)
Semantic verbal fluency	17	19.2 (2.3)
Rey complex figure test		
Immediate copy	36	35.4 (0.5)
Delayed recall	18	20.1 (5.6)
Wisconsin Card Sorting Test (modified version)		
Categories	6	5.5 (0.6)
Perseverative errors	2	2.2 (0.3)
Other errors	5	0.5 (0.1)
Pyramid & Palm Tree	51	51.8 (0.4)

Social Executive Assessment	Patient	Controls (n=14)
Faux Pas	14	19.0 (1.5)
Hotel Task		
Tasks attempted	3	4.5 (0.5)
Tasks correct	3	4.4 (0.5)
Time deviation	735 s	277 (130)
Button pressing	1	1.9 (0.3)
Garage time deviation	2	4.1 (2.4)
Mind in the Eyes Test	11	14.8 (1.4)
Multiple Errands Test – hv		
Inefficiencies	4	0.8 (1.1)
Rule breaks	5	1.0 (1.2)
Interpretation failures	1	0.1 (0.3)
Task failures	2	0.2 (0.4)

Iowa Gambling Test performance. Mean (\pm standard error of the mean) net score on each block of 20 cards for the control group, the bvFTD group, and the case patient's performance at presentation and 2 years later. (Manes et al., 2010)

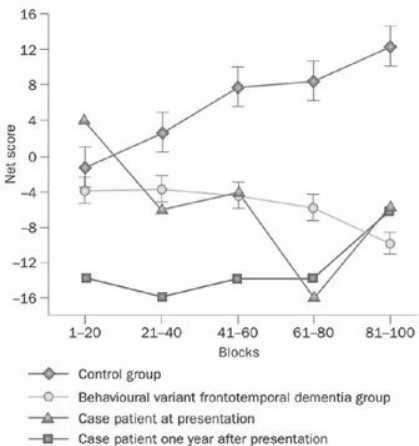


Figure 9.3 bvFTD Case Study M.C (MRI scan and neuropsychological profile).

Manes FF, Torralva T, Roca M, Gleichgerrcht E, Bekinschtein TA, Hodges JR. Frontotemporal dementia presenting as pathological gambling. *Nat Rev Neurol.* 2010;6:347-52. With permission.

Language

It is by now clear that the greatest deficits in bvFTD patients appear to be in the domains of executive functions, attention, and some types of memory but

it is important to check also other domains such as language. Although the language variants of FTD have the greatest deficits in the language domain, patients with bvFTD should be assessed with a short language battery too. It is important to consider that if any of the language tests appear to be impaired, a more comprehensive language battery should be utilized to understand the profile more fully. No specific tests will be explained in this section as they will be explained in detail in the next section of this chapter.

Language variants of FTD

As described in detail in [Chapter 5](#), three variants of primary progressive aphasia (PPA) are described: PNFA, semantic variant progressive aphasia (svPPA), which is also referred to as “semantic dementia” (SD), and LPA [\[79\]](#). In recent years many tests and batteries have been developed to assess patients with suspected PPA. Patients with PPA may present with very different linguistic abnormalities. They may have difficulties in word retrieval, in understanding the meaning of words, or in speech patterns or the production of grammatically correct sentences. Thus, tests of word comprehension, speech production (fluency, naming, and repetition), and also oral reading (to detect surface dyslexia) and writing (to detect surface agraphia) should be assessed in the three variants of PPA.

Semantic memory

This long-term memory system is severely affected in SD, in contrast with PNFA and LPA (e.g., [\[79, 80\]](#)). Semantic tests assess long-term memory for facts, objects, and concepts as well as words and their meaning [\[81\]](#). Semantic memory is usually assessed with tasks such as picture naming,

defining spoken or written words, picture matching, category fluency tests, semantic judgments, analogies, or associative semantic tests [81].

The most frequent tests used to assess semantic memory skills are the Pyramids and Palm Trees Test [82], Cambridge Semantic Memory Test Battery [83], Repeat and Point [84], Kissing and Dancing Test [85], or the Words and Sentences (oral or written) Picture Matching tasks from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) [86].

Pyramids and Palm Trees Test (PPT):

This is the most widely used test to assess semantic memory. The aim of this assessment is to associate a picture (or a word) with another picture; for example, a pyramid is associated with a palm tree rather than a pine tree. This test contains 52 specimens, and has different administration modalities: pictorial, verbal, and combined. The three-picture modality is, however, the most commonly used. *This is very useful to detect semantic problems. SD patients will have many problems in this test, also, in the early stages of the diseases. LPA and PNFA will resolve this test without problems.*

Cambridge Semantic Memory Test Battery:

This is a battery specifically developed to diagnose a specific semantic category deficit. Nevertheless, this battery fails to differentiate between patients with SD and AD. The authors use 64 items, 32 living things (animals and fruits) and 32 man-made (e.g., transport). The same items are used to evaluate conceptual information across different input and output modalities. The different subtests are: category fluency, picture naming, matching word–picture, pictures and words sorting according to different semantic complexity levels, and a word definition task. This battery also includes an associative semantic test, the Camel and Cactus Test (CCT). This test is similar to the PPT, but it has several differences: in the PPT the subject has to choose one

of the two possibilities, instead in the CCT, subjects have to select one of four possibilities, so they have less chances of selecting without knowledge.

Another advantage of this test is that this subtest assesses the same 64 items and it has colored pictures. This is a notable difference from other semantic tests because color is an important semantic attribute [87].

Repeat and Point Test:

This is a quick measure to differentiate between SD and PNFA. This test contains 10 items and has 2 aims. First of all, participants have to repeat a word (which represents a concrete noun). Once they repeat it, they have to select a picture that represents the target word. The subject has to choose between seven pictures that are semantically and perceptually similar. *SD patients could repeat words without problems but they will fail in the matching part. PNFA patients have the opposite pattern. They have repetition problems but they could match word–picture correctly* [84].

Kissing and Dancing Test (KDT):

This is another associative semantic test and contains the same number of triads as the PPT. The aim of this test is to assess the knowledge of actions and verbs. The authors considered the KDT to be an extension of the PPT. A comparison between the two tests allows the diagnosis of possible dissociations between grammatical categories (nouns/verbs) and semantic categories (objects/actions). *Bak and Hodges compared SD in PPT and KDT, and found that patients had poor performance on both batteries* [85].

Word (oral or written) Picture Matching. Psycholinguistic Assessment of Language Processing in Aphasia (PALPA):

This is another kind of test assessing concrete knowledge. The patient must match a word (oral or written) with a picture that represents it out of five possibilities (the target, a near-related semantic distracter, a distant-related semantic distracter, a visual distracter, and an unrelated picture). The picture

selected can allow different types of semantic impairments to be identified [86].

Sentences (oral or written) Picture Matching. Psycholinguistic Assessment of Language Processing in Aphasia (PALPA):

These tasks allow for the assessment of sentence comprehension. Different grammatical structures are presented. *LPA patients, because of the problems in auditory verbal short-term memory, will have deficits in sentences comprehension [80]. PNFA patients also have difficulty with grammatical comprehension for complex grammatical constructions [88].*

Semantic fluency

Another task to assess semantic memory is categorical fluency. In this task the participants have to say as many words as possible in a given time, usually 60 seconds, from a semantic category (e.g., animals) [89]. *In SD these capacities are severely affected, but phonologic fluency is relatively spared, at least during the early stages of the disease [90]. SD patients have many difficulties with certain specific semantic categories (e.g., “breeds of dog”) and relatively preserved performance in others (e.g., vehicles).*

The semantic fluency test is a quick and easy task and presents high sensitivity and specificity for the diagnosis of dementia.

Synonym judgments

Synonym judgments. Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) [86]:

The aim of this task is for the subject to judge whether two words (oral or written) are similar. This is a test of both concrete (e.g., marriage–wedding)

and abstract (e.g., advice–suggestion) word processing. *It has been assumed that SD patients tend to have better comprehension of abstract words [91], nevertheless some other researchers have detected better comprehension of concrete words [92]. In most aphasic patients, concrete words are comprehended more successfully than abstract words. This is known as the “typical concreteness effect.”*

Naming

Subjects have to activate a specific word represented by a picture, an object, or an oral definition.

The Boston Naming Test [93]:

This is the most used test to evaluate oral naming. This test contains 60 stimuli ranging according to lexical frequency. The patient should tell the examiner the name of each picture in 20 seconds. After this time, the examiner gives a semantic or a phonemic cue (semantic information or the initial sound of the target word) to help the subject. If the patient responds after the phonemic cue, the answer is not counted in the final score. *Most aphasic patients have difficulties in recovering words and have problems with picture or object naming tests. This is a common symptom in the three variants of PPA (e.g., [94]). Nevertheless, they differ in the level of impairment and in the types of error they produce. Anomia is an important symptom in SD. These patients have many problems in recovering the correct word and they typically produce a semantic error. They might have a tendency to activate the name of a superordinate category: for example, individuals might say “animal” instead of “penguin,” a coordinate (e.g., individuals might say “eagle” instead of “falcon”), or the prototype member of a category (e.g., individuals might say “dog” or “cat” for all the animals). Hodges et al. studied the progression in SD patients [90], showing that in the early stages patients may use a word that represents another member of the same*

category (coordinate error), later they produce the name of a prototype member of the category and, finally, they only activate the superordinate category name. In addition, SD patients produce some vague expressions such as “I don’t remember,” “I don’t know,” as well as circumlocution without semantic content. LPA patients also have anomia and they have pauses or latencies and phonemic paraphasias when they try to find a word. Difficulty in naming is a feature commonly found in PNFA, but is less severe than in SD and LPA. LPA patients have phonologic errors or phonemic approximations but they know the meaning of the words [80] (see case presentation in [Figure 9.4](#)).

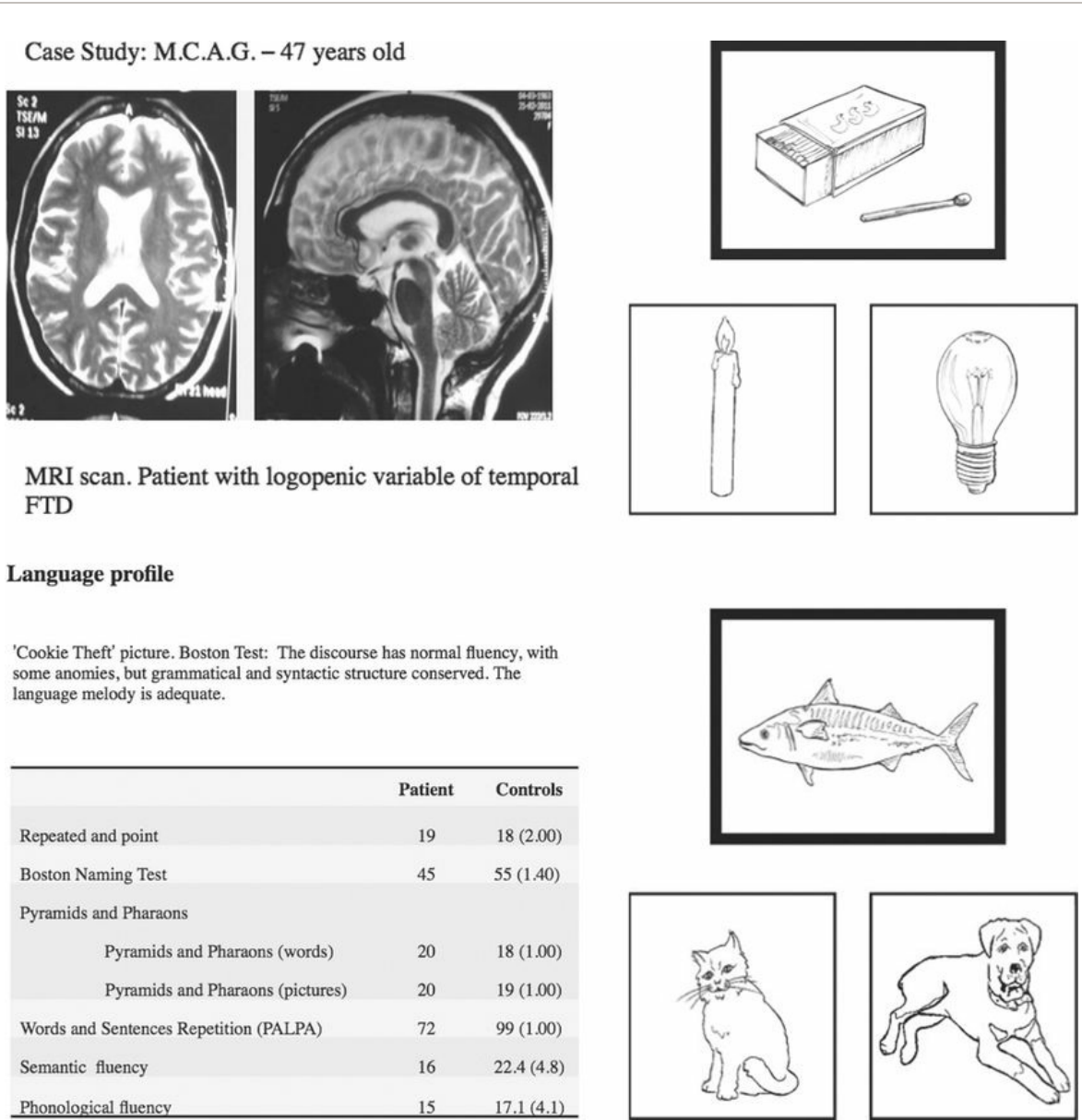


Figure 9.4 Case Study M.C.A.G (MRI scan and language profile).

From: Manes, F. F. *et al.*, *Nat Rev Neurol*. 2010;6:347, with permission.

Reading

Word reading:

The Cambridge Semantic Memory Test Battery [83] assesses oral reading and writing with the same 64 stimuli used in the others' subtests. These target words have regular and irregular spelling so that they are suitable for evaluating the surface dyslexia. *A typical symptom of SD is surface dyslexia. SD patients have problems reading irregular words because they pronounce them as they are spelled. That is, they rely on rules of regular letter-sound correspondence rather than semantic memory of irregular pronunciations, thus making regularization errors [95].*

Reading Tests. Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) [86]:

In this battery there are two subtests to assess oral reading: Word Reading (Regular and Irregular) and Non-Word Reading. *SD patients with surface dyslexia will produce regularization errors when they have to read irregular words [96, 97]. The LPA variant has a pattern of phonologic dyslexia, that is, a deficit in non-word reading with lexical errors. Both patterns of error are frequently seen in these subtypes of PPA and are considered as part of the diagnostic criteria.*

Repetition

Words and Sentences Repetition. Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) [86].

PNFA patients have difficulty repeating words and non-words, while LPA patients have difficulty repeating sentences. Five tasks of the battery assess repetition abilities (four are designed to evaluate words and non-word repetition and one is suitable to assess sentence repetition). *PNFA patients have more difficulty with long words or with complex consonant clusters. These patients will produce phonemic (phoneme omissions, transpositions, or additions) and phonetic errors (speech sound distortions and other abnormalities of articulation) while SD patients will conserve this capacity until the last stages of the illness* [80].

Oral production

“Cookie Theft” picture. Boston Test [98]:

The patterns of oral speech production impairments in the three PPA variants are very different. SD patients have fluent speech but produce semantic errors in spontaneous speech. *This pattern can be observed in the use of vague language without semantic content: SD patients produce words like “thing” or “that”* [99]. *PNFA patients have a dysfluent speech, usually with marked effort. They produce short sentences with a very simple structure and grammatical errors are frequent in their speech. LPA patients have a phonologic short-term memory deficit, so they will have variable difficulties in producing grammatically complex sentences* [100], *and will pause to find words because of lexical retrieval difficulties.*

Conclusions

The aim of the present chapter was to summarize some of the instruments (tests and batteries) usually used to capture neuropsychological deficits in FTD patients. Numerical scores on these tests alone are of limited value in

differentiating FTD from other dementias, but performance characteristics and error types can be helpful in distinguishing FTD from other types of dementia. Qualitative information should be included in neuropsychological research and clinical assessments for both the language and behavioral variants. Although testing all domains is important, incorporating more “comprehensive” tests of executive, social, and emotional functions in the neuropsychological assessment battery is at the moment one of the most important challenges of the FTD scientific community. Most of these tasks are still in the research arena, but hopefully the use of such standardized “bespoke” neuropsychological batteries will eventually become “routine” in clinic.

References

1. Folstein MF, Folstein SE, McHugh PR. “Mini-mental.” A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98.

2. Mathuranath PS, Nestor PJ, Berrios GE, *et al.* A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000;**55**(11):1613–20.

3. Mioshi E, Dawson K, Mitchell J, *et al.* The Addenbrookes's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* 2006;**21**:1078–85.

4. Hsieh S, Irish M, Daveson N, Hodges JR, Piguet O. When one loses empathy: its effect on carers of patients with dementia. *J Geriatr Psychiatry Neurol* 2013;**26**(3):174–84.

5. Wechsler D. *Wechsler Adult Intelligent Scale III [Manual]*, 3rd edn. San

Antonio, TX: The Psychological Corporation, 1997.

6. Golden, CJ. *Stroop, Test de Colores y Palabras. Manual de Aplicación* Madrid: TEA Ediciones, 1999.

7. Partington JE, Leiter RG. Partington's pathway test. *Psychol Serv Bull* 1949;**1**:9–20.

8. Conners CK. *Conners' Continuous Performance Test II: Computer Program for Windows Technical Guide and Software Manual* New York: Mutli-Health Systems, 2000.

9. Torralva T, Roca M, Gleichgerrcht E, *et al.* A neuropsychological battery of detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain* 2009;**132**:1299–309.

10. Florance HV, Stopford AP, Kalapothakis JM, *et al.* Evidence for α -helices in the gas phase: a case study using Melittin from honey bee venom. *Analyst* 2011;**136**(17):3446–52.

11. Collette F, Amieva H, Adam S, *et al.* Comparison of inhibitory functioning in mild Alzheimer's disease and frontotemporal dementia. *Cortex* 2007;**43**(7):866–74.

12. Hutchinson AD, Mathias JL. Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. *J Neurol Neurosurg Psychiatry* 2007;**78**(9):917–28.

13. Hodges JR, Davies R, Xuereb J, *et al.* Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* 2004;**56**:399–406.

14. Hornberger M, Savage S, Hsieh S, *et al.* Orbitofrontal dysfunction discriminates behavioral variant frontotemporal dementia from Alzheimer's disease. *Dement Geriatr Cogn Disord* 2010;**30**(6):547–52.

-
- 15.** Glosser G, Gallo JL, Clark CM, Grossman M. Memory encoding and retrieval in frontotemporal dementia and Alzheimer's disease. *Neuropsychology* 2002;**16**(2):190–6.
-
- 16.** Kramer J, Jurik J, Sha SJ, *et al.* Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer's disease. *Cogn Behav Neurol* 2003;**16**:211–18.
-
- 17.** Rogers TT, Hocking J, Noppeney U, *et al.* Anterior temporal cortex and semantic memory: reconciling findings from neuropsychology and functional imaging. *Cogn Affect Behav Neurosci* 2006;**6**(3):201–13.
-
- 18.** Rascovsky K, Salmon DP, Hansen LA, *et al.* Disparate letter and semantic category fluency deficits in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *Neuropsychology* 2007;**21**(1):20–30.
-
- 19.** Hou CE, Miller BL, Kramer JH. Patterns of autobiographical memory loss in dementia. *Int J Geriatr Psychiatry* 2005;**20**(9):809–15.
-
- 20.** Rey A. L'examen physiologique dans le cas d'encephalopathie traumatique. *Arch Psychol (Geneve)* 1941;**28**:286–340.
-
- 21.** Blackwell AD, Sahakian BJ, Vesey R, *et al.* Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. *Dement Geriatr Cogn Disord* 2004;**17**(1–2):42–8.
-
- 22.** Grober E, Buschke H, Crystal H, *et al.* Screening for dementia by memory testing. *Neurology* 1988;**38**:900–3.
-
- 23.** Kopelman MD, Wilson BA, Baddeley AD. The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J Clin Exp Neuropsychol* 1989;**11**(5):724–44.
-
- 24.** Groot YC, Wilson BA, Evans J, Watson P. Prospective memory functioning

in people with and without brain injury. *J Int Neuropsychol Soc* 2002;**8**(5):645–54.

25. Perri R, Fadda L, Caltagirone C, Carlesimo GA. Word list and story recall elicit different patterns of memory deficit in patients with Alzheimer's disease, frontotemporal dementia, subcortical ischemic vascular disease, and Lewy body dementia. *J Alzheimers Dis* 2013;**37**(1):99–107.

26. Lee AC, Rahman S, Hodges JR, *et al.* Associative and recognition memory for novel objects in dementia: implications for diagnosis. *Eur J Neurosci* 2003;**18**(6):1660–70.

27. Sarazin M, Chauviré V, Gerardin E, *et al.* The amnesic syndrome of hippocampal type in Alzheimer's disease: an MRI study. *J Alzheimers Dis* 2010;**22**(1): 285–94.

28. Greene JD, Hodges JR, Baddeley AD. Autobiographical memory and executive function in early dementia of Alzheimer type. *Neuropsychologia* 1995;**33**(12):1647–70.

29. Thomas-Antérion C, Jacquin K, Laurent B. Differential mechanisms of impairment of remote memory in Alzheimer's and frontotemporal dementia. *Dement Geriatr Cogn Disord* 2000;**11**(2):100–6.

30. Kamminga J, O'Callaghan C, Hodges JR, Irish M. Differential prospective memory profiles in frontotemporal dementia syndromes. *J Alzheimers Dis* 2014;**38**(3):669–79.

31. Gasparini MA. Descriptive study on constructional impairment in frontotemporal dementia and Alzheimer's disease. *Eur J Neurol* 2008;**15**:589–97.

32. Possin KL, Laluz VR, Alcantar OZ, *et al.* Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. *Neuropsychologia*

2011;**49**:43–8.

33. Osterrieth PA. “File test de copie d' une figure complex: Contribution al'etude de la perception et de la memoire [The test of copying a complex figure: a contribution to the study of perception and memory].” *Arch Psychol (Geneve)* 1944;**30**:286–356.

34. Warrington EK, James M. *The Visual Object and Space Perception Battery* Bury St Edmunds, England: Thames Valley Test Company, 1991.

35. Clague F, Dudas RB, Thompson SA, *et al.* Multidimensional measures of person knowledge and spatial associative learning: can these be applied to the differentiation of Alzheimer's disease from frontotemporal and vascular dementia? *Neuropsychologia* 2005;**43**(9):1338–50.

36. Possin KL, Feigenbaum D, Rankin KP, *et al.* Dissociable executive functions in behavioral variant frontotemporal and Alzheimer dementias. *Neurology* 2013;**80**(24):2180–5.

37. Pose M, Cetkovich M, Gleichgerrcht E, *et al.* The overlap of symptomatic dimensions between frontotemporal dementia and several psychiatric disorders that appear in late adulthood. *Int Rev Psychiatry* 2013;**25**(2):159–67.

38. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000;**55**(11):1621–6.

39. Torralva T, Roca M, Gleichgerrcht E, *et al.* INECO Frontal Screening (IFS): a brief, sensitive, and specific tool to assess executive functions in dementia. *J Int Neuropsychol Soc* 2009;**15**(5):777–86.

40. Kleinhans N, Akshoomoff N, Delis DC. Executive functions in autism and Asperger's disorder: flexibility, fluency, and inhibition. *Dev Neuropsychol* 2005;**27**(3):379–401.

41. Nelson H. A modified card sorting response sensitive to frontal lobe defects.

Cortex 1976;**12**:313–24.

42. Cullbertson WC, Zillmer EA. *Tower of London. Technical Manual*, 2nd edn. Toronto, Drexel University: Multi-Health System Inc., 2005.

43. Burgess PW, Shallice T. *The Hayling Test and Brixton Tests* Thurston, Suffolk: Thames Valley Test Company, 1997.

44. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System* San Antonio, TX: The Psychological Corporation, 2001.

45. Harciarek M, Cosentino S. Language, executive function and social cognition in the diagnosis of frontotemporal dementia syndromes. *Int Rev Psychiatry* 2013;**25**(2):178–96.

46. Ringman JM, Kwon E, Flores DL, *et al.* The use of profanity during letter fluency tasks in frontotemporal dementia and Alzheimer disease. *Cogn Behav Neurol* 2010;**23**(3):159–64.

47. Davis C, Heidler-Gary J, Gottesman RF, *et al.* Action versus animal naming fluency in subcortical dementia, frontal dementias, and Alzheimer's disease. *Neurocase* 2010;**16**(3):259–66.

48. Libon DJ, Xie SX, Moore P, *et al.* Patterns of neuropsychological impairment in frontotemporal dementia. *Neurology* 2007;**68**(5):369–75.

49. Hornberger M, Piguet O, Kipps C, Hodges JR. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology* 2008;**71**:1481–8.

50. Shallice T. Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci* 1982;**298**(1089):199–209.

51. Possin KL, Chester SK, Laluz V, *et al.* The frontal-anatomic specificity of design fluency repetitions and their diagnostic relevance for behavioral variant

frontotemporal dementia. *J Int Neuropsychol Soc* 2012;**18**(5):834–44.

52. Torralva T, Kipp CM, Hodges JR, *et al.* The relationship between affective decision-making and theory of mind in the frontal variant of frontotemporal dementia. *Neuropsychologia* 2007;**45**:342–9.

53. Gregory C, Lough S, Stone VE, *et al.* Theory of mind in frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain* 2002;**125**:752–64.

54. Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. *J Cogn Neurosci* 1998;**10**:640–56.

55. Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M. A further advanced test of theory of mind: evidence from very high functioning adults with autism or Asperger syndrome. *J Child Psychol Psychiatry* 1997;**38**:813–22.

56. Golan O, Baron-Cohen S, Hill J. The Cambridge Mindreading (CAM) face-voice battery: testing complex emotion recognition in adults with and without Asperger syndrome. *J Autism Dev Disord* 2006;**36**(2):169–83.

57. Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M. Another advanced test of theory of mind: evidence from very high functioning adults with autism or Asperger Syndrome. *J Child Psychol Psychiatry* 1997;**38**:813–22.

58. Perner J, Wimmer H. “John thinks that Mary thinks that” attribution of second-order false beliefs by 5- to 10-year-old children. *J Exp Child Psychol* 1985;**39**:437–71.

59. Freedman M, Binns MA, Black SE, *et al.* Theory of mind and recognition of facial emotion in dementia: challenge to current concepts. *Alzheimer Dis Assoc Disord* 2013;**27**(1):56–61.

60. Fernandez-Duque D, Baird JA, Black SE. False-belief understanding in frontotemporal dementia and Alzheimer's disease. *J Clin Exp Neuropsychol*

2009;**31**(4):489–97.

61. Lough S, Kipps CM, Treise C *et al.* Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia* 2006;**44**(6):950–8.

62. Happe FG. An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *J Autism Dev Disord* 1994;**24**:129–54.

63. McDonald S, Bornhofen C, Shum D, *et al.* Reliability and validity of The Awareness of Social Inference Test (TASIT): a clinical test of social perception. *Disabil Rehabil* 2006;**28**:1529–42.

64. Ekman P, Friesen E. *Pictures of Facial Affects* Palo Alto, CA: Consulting Psychologists Press, 1976

65. Young AW, Rowland D, Calder AJ, *et al.* Facial expression megamix: tests of dimensional and category accounts of emotion recognition. *Cognition* 1997;**63**:271–313.

66. Davis MH. Measuring individual differences in empathy. Evidence for multidimensional approach. *J Pers Soc Psychol* 1993;**44**:113–26.

67. Savage SA, Lillo P, Kumfor F, *et al.* Emotion processing deficits distinguish pure amyotrophic lateral sclerosis from frontotemporal dementia. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;**15**(1–2):39–46.

68. Rankin KP, Gorno-Tempini ML, Allison SC, *et al.* Structural anatomy of empathy in neurodegenerative disease. *Brain* 2006;**129**:2945–56.

69. Kipps CM, Nestor PJ, Acosta-Cabronero J, *et al.* Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing. *Brain* 2009;**132**:592–603.

70. Kumfor F, Piguet O. Disturbance of emotion processing in frontotemporal

dementia: a synthesis of cognitive and neuroimaging findings. *Neuropsychol Rev* 2012;**22**(3):280–97.

71. Diehl-Schmid J, Pohl C, Ruprecht C, *et al.* The Ekman 60 Faces Test as a diagnostic instrument in frontotemporal dementia. *Arch Clin Neuropsychol* 2007;**22**(4):459–64.

72. Perry RJ, Rosen HR, Kramer JH, *et al.* Hemispheric dominance for emotions, empathy and social behaviours: evidence from right and left handers with frontotemporal dementia. *Neurocase* 2001;**7**:145–60.

73. Gleichgerricht E, Torralva T, Roca M, *et al.* The role of social cognition in moral judgment in frontotemporal dementia. *Soc Neurosci* 2010;**6**(2):113–22.

74. Burgess P. Development of a simplified version of the multiple errands test for use in hospital settings. *Neuropsychol Rehabil* 2002;**12**:231–55.

75. Manly T, Hawkins K, Evans J, *et al.* Rehabilitation of executive function: facilitation of effective goal management on complex tasks using periodic auditory alerts. *Neuropsychologia* 2002;**40**(3):271–81.

76. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;**50**(1–3):7–15.

77. Funkiewiez A, Bertoux M, de Souza LC, *et al.* The SEA (Social cognition and Emotional Assessment): a clinical neuropsychological tool for early diagnosis of frontal variant of frontotemporal lobar degeneration. *Neuropsychology* 2012;**26**(1):81–90.

78. Bertoux M, Delavest M, de Souza LC, *et al.* Social Cognition and Emotional Assessment differentiates frontotemporal dementia from depression. *J Neurol Neurosurg Psychiatry* 2012;**83**(4):411–16.

79. Gorno-Tempini ML, Hillis AE, Weintraub S, *et al.* Classification of primary

progressive aphasia and its variants. *Neurology* 2011;**76**(11):1006–14.

80. Bonner MF, Ash S, Grossman M. The new classification of primary progressive aphasia into semantic, logopenic, or nonfluent/agrammatic variants. *Curr Neurol Neurosci Rep* 2010;**10**(6):484–90.

81. Patterson K, Hodges JR. Disorders of semantic memory. In A. Baddley, B. Wilson, F. Watts eds. *Handbook of Memory Disorders* Chichester: John Wiley. 1995;167–86.

82. Howard D, Patterson K. *Pyramids and Palm Trees: A Test of Semantic Access from Words and Pictures* Bury St Edmunds, Suffolk: Thames Valley Test Company, 1992.

83. Adlam AL, Patterson K, Bozeat S, Hodges JR. The Cambridge Semantic Memory Test Battery: detection of semantic deficits in semantic dementia and Alzheimer's disease. *Neurocase* 2010;**16**(3):193–207.

84. Hodges JR, Martinos M, Woollams AM, *et al.* Repeat and Point: differentiating semantic dementia from progressive non-fluent aphasia. *Cortex* 2008;**44**(9):1265–70.

85. Bak TH, Hodges JR. Kissing and dancing – a test to distinguish the lexical and conceptual contributions to noun/verb and action/object dissociation. Preliminary results in patients with frontotemporal dementia. *J Neurolinguist* 2003;**16**(2–3):169–81.

86. Kay J, Lesser R, Coltheart M. *PALPA – Psycholinguistic Assessments of Language Processing in Aphasia* Hove (East Sussex): Psychology Press (Taylor & Francis Group), 1992.

87. Rogers TT, Patterson K, Graham K. Colour knowledge in semantic dementia: it is not all black and white. *Neuropsychologia* 2007;**45**:3285–98.

88. Peelle JE, Cooke A, Moore P, Vesely L, Grossman M. Syntactic and

thematic components of sentence processing in progressive nonfluent aphasia and nonaphasic frontotemporal dementia. *J Neurolinguist* 2007;**20**:482–94.

89. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment* New York: Oxford University Press, 2004.

90. Hodges JR, Graham N, Patterson K. Charting the progression in semantic dementia: implications for the organization of semantic memory. *Memory* 1995;**3**(3–4):463–95.

91. Breedin S, Saffran E, Coslett H. Reversal of the concreteness effect in a patient with semantic dementia. *Cogn Neuropsychol* 1994;**11**:617–60.

92. Hoffman P, Jones RW, Lambon Ralph MA. Be concrete to be comprehended: consistent imageability effects in semantic dementia for nouns, verbs, synonyms and associates. *Cortex* 2013;**49**:1206–18.

93. Kaplan E, Googlass H, Weintraub S. *Boston Naming Test* Philadelphia: Lea & Febiger, 1983.

94. Harciarek M, Kertesz A. Primary progressive aphasias and their contribution to the contemporary knowledge about the brain-language relationship. *Neuropsychol Rev* 2011;**21**(3):271–87.

95. Jefferies E, Lambon Ralph MA, Jones R, Bateman D, Patterson K. Surface dyslexia in semantic dementia: a comparison of the influence of consistency and regularity. *Neurocase* 2004;**20**(4):290–9.

96. Patterson K, Lambon Ralph MA, Jefferies E, *et al.* ‘Pre-semantic’ cognition in semantic dementia: six deficits in search of an explanation. *J Cogn Neurosci* 2006;**16**:169–83.

97. Woollams AM, Lambon Ralph MA, Plaut DC, Patterson K. SD-squared: on the association between semantic dementia and surface dyslexia. *Psychol Rev* 2007;**114**(2):316–39.

98. Goodglass H, Kaplan E. *Assessment of Aphasia and Related Disorders* Philadelphia: Lea & Febiger, 1976.

99. Meteyard L, Quinn E, Patterson K. Ever decreasing circles: speech production in semantic dementia. *Cortex* 2014;**55**:17–29.

100. Gorno-Tempini ML, Brambati SM, Ginex V, *et al.* The logopenic/phonological variant of primary progressive aphasia. *Neurology* 2008;**71**:1227–34.

Chapter 10

Imaging of frontotemporal dementia



Jonathan D. Rohrer

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Frontotemporal dementia (FTD) is a clinically, genetically, and pathologically heterogeneous neurodegenerative disorder. This heterogeneity makes diagnosis difficult during life, with poor correlation between the clinical syndrome and the underlying genetic or pathologic cause. Neuroimaging studies have aimed to improve these correlations by identifying neuroanatomical signatures associated with particular clinical syndromes, genetic mutations, or underlying pathologies. The sections in this chapter will therefore focus on each of these in turn. Within each section, findings seen using magnetic resonance imaging (MRI) techniques will be discussed first followed by those found with single-photon emission tomography (SPECT) and positron emission tomography (PET) imaging.

Structural T1 MRI has been the key technique for understanding the neuroimaging features of FTD in the research literature over the last 20 years. A number of different methods have been used to analyze these data,

from simple visual rating scales, through methods of measuring the volumes of specific regions of interest (ROIs; e.g., the frontal lobes), to more complex statistical techniques such as voxel-based morphometry (VBM). Each section will therefore focus initially on the findings in T1 MR imaging before reviewing the smaller literature in other MRI sequences, namely diffusion tensor imaging (DTI), resting state functional MRI (rsfMRI), and arterial spin labeling (ASL) perfusion MRI. Findings in SPECT and fluorodeoxyglucose positron emission tomography (FDG-PET) imaging will then be discussed as well as more novel types of PET imaging, particularly those using ligands binding to proteins involved in neurodegenerative disorders (amyloid and tau).

Clinical syndromes

Behavioral variant FTD (bvFTD)

Early imaging studies in bvFTD showed evidence of an anterior pattern of atrophy or hypometabolism in the brain affecting the frontal lobes and the anterior temporal lobes, with many noting that this pattern was often asymmetric [[1–3](#)]. Following this early work, a number of neuroimaging studies attempted to identify more specific areas within the frontal and temporal lobes that were associated with a clinical diagnosis of bvFTD. A meta-analysis of this literature identified a set of (mostly right hemisphere) areas including parts of the frontal lobe (anterior medial frontal, gyrus rectus, and superior frontal) as well as areas outside the frontal lobes: anterior cingulate, anterior insula, and thalamus [[4, 5](#)]. However this study investigated patients with a wide range of disease severity: mean Mini-Mental State Examination (MMSE) in the studies that were included varied between 14 and 25, with mean disease duration between 2 and 4 years.

Another study separated patients into three different stages using the Clinical Dementia Rating (CDR): an early group with CDR 0.5 and two other groups with CDR 1 and CDR 2–3 [6]. In the early group, atrophy involved areas in the frontal lobe (rostromedial frontal, frontal pole, dorsolateral frontal, and orbitofrontal) as well as anterior cingulate, anterior insula, hippocampus, and subcortical areas (ventral striatum and dorsomedial thalamus) (Figure 10.1). Atrophy was bilateral but right hemisphere involvement was greater than left. With greater CDR score atrophy became more extensive in the same areas, particularly within the frontal lobe, with spread to more posterior areas including posterior insular, temporal, and anterior parietal lobes (Figure 10.1). A study of pathologically confirmed bvFTD patients separated by CDR found very similar results (Figure 10.2) [7]. Further studies have suggested that these areas affected in early disease (frontal-insula-anterior cingulate) are part of a structurally and functionally connected neural network that is particularly vulnerable in bvFTD and that has a histopathologic correlate in the form of selectively vulnerable von Economo neurons [8].

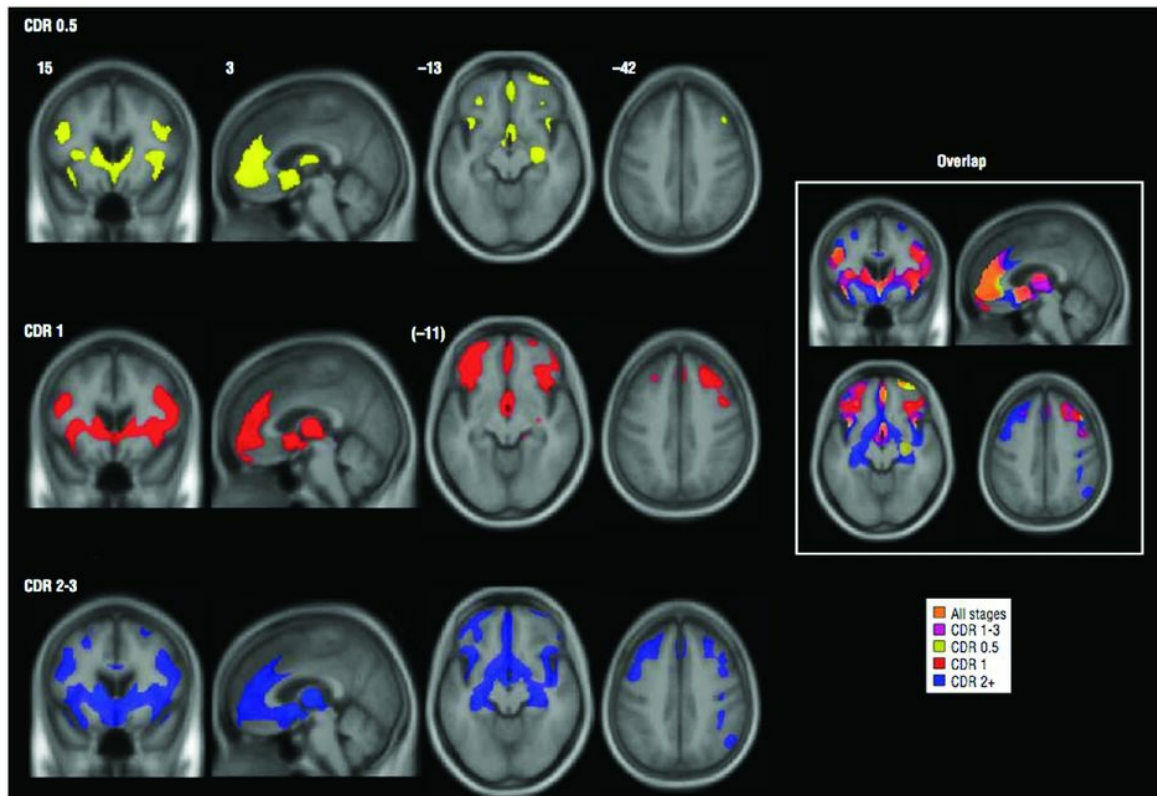


Figure 10.1 Regional brain atrophy across three clinical stages of behavioral variant FTD. In the group with very mild dementia (CDR 0.5), atrophy involved areas in the frontal lobe (rostromedial frontal, frontal pole, dorsolateral frontal, and orbitofrontal) as well as anterior cingulate, anterior insula, hippocampus, and subcortical areas (ventral striatum and dorsomedial thalamus). The right hemisphere was more prominently involved than the left. In the group with mild dementia (CDR 1), atrophy became more extensive in the same areas, particularly within the frontal lobe, with spread to more posterior areas including posterior insula, temporal, and anterior parietal lobes. In moderate to severe FTD dementia (CDR 2–3), atrophy continued to extend beyond the areas originally involved.

Figure used with permission from Seeley WW, Crawford R, Rascofsky K, *et al.* (2008). Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Archives of Neurology*, 65(2), 249–55.

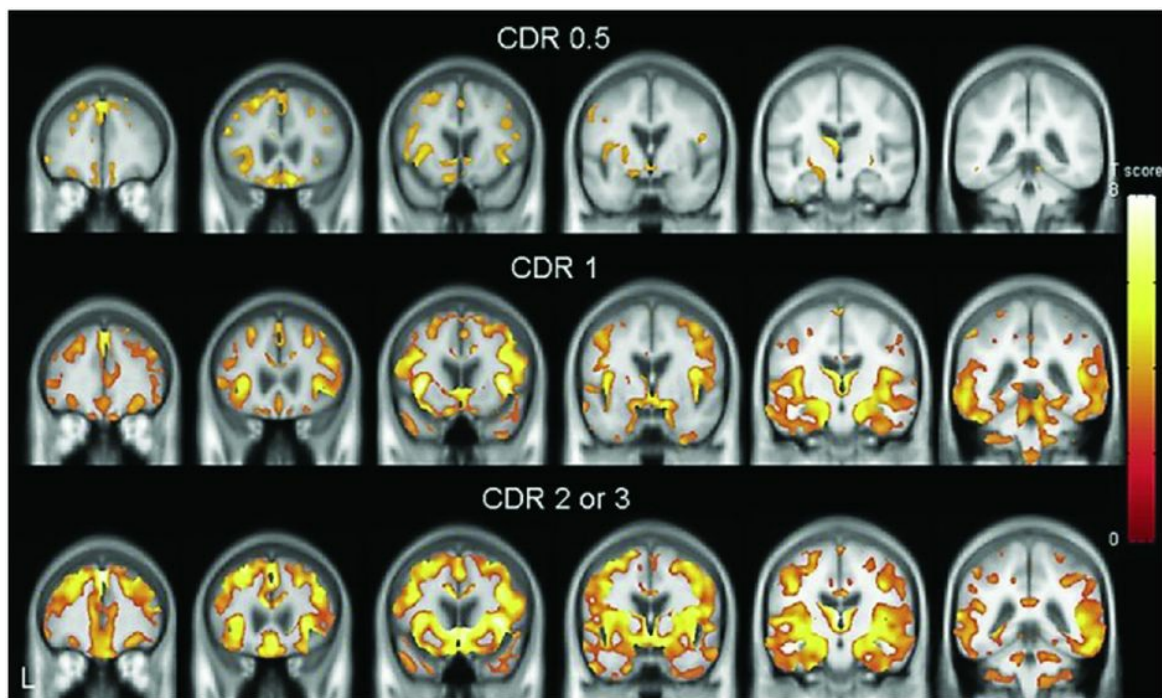


Figure 10.2 A study of pathologically confirmed bvFTD patients separated by CDR found very similar results to those in [Figure 10.1](#). Further studies have suggested that these areas affected in early disease (frontal-insula-anterior cingulate) are part of a structurally and functionally connected neural network that is particularly vulnerable in bvFTD and that has a histopathologic correlate in the form of selectively vulnerable von Economo neurons.

Figure used with permission from Whitwell JL, Jack CR Jr, Senjem ML, *et al.* (2009). MRI correlates of protein deposition and disease severity in postmortem frontotemporal lobar degeneration. *Neurodegenerative Diseases*, 6(3), 106–17.

However, bvFTD is pathologically heterogeneous and it is unclear whether this same network is affected in all groups independent of the underlying pathology. One study performed a cluster analysis which suggested that bvFTD can be divided into four separate neuroanatomical groups: frontal dominant, temporal dominant, frontotemporal and temporofrontoparietal ([Figure 10.3](#)) [9]. In a subgroup of patients in this study who had come to post-mortem there were no clear correlations between imaging features and pathologic subtype apart from the temporal-

dominant group who all had mutations in the *MAPT* gene. Further work needs to be done to see whether these four groups map on to separate brain networks (or subsystems within the same network).

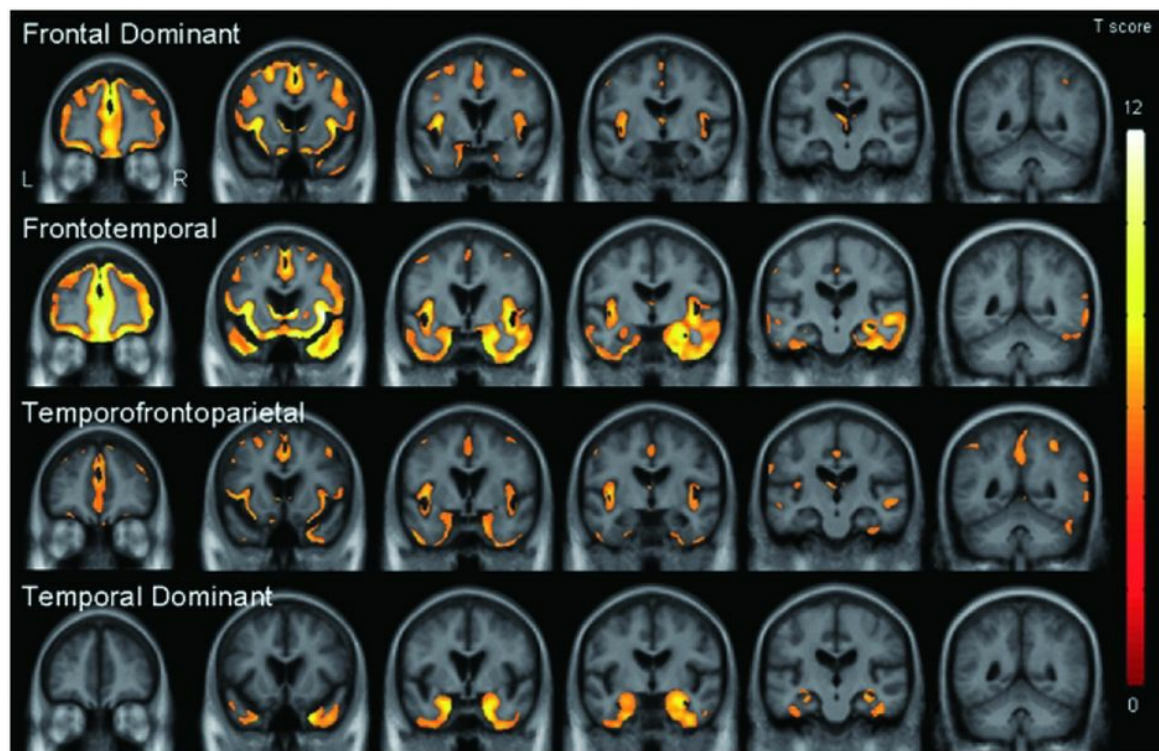


Figure 10.3 One study performed a cluster analysis which suggested that bvFTD can be divided into four separate neuroanatomical groups: frontal dominant, temporal dominant, frontotemporal and temporofrontoparietal. In a subgroup of patients in this study who had come to post-mortem there were no clear correlations between imaging features and pathological subtype apart from the temporal-dominant group who all had mutations in the *MAPT* gene. Further work needs to be done to see whether these four groups map on to separate brain networks (or subsystems within the same network).

Figure used with permission from Whitwell JL, Przybelski SA, Weigand SD, *et al.* (2009). Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. *Brain*, 132(Pt 11), 2932–46.

Longitudinal T1 MRI studies of bvFTD have been performed less frequently but such studies show an elevated rate of whole-brain atrophy [10, 11].

Other MR sequences have been investigated to a lesser extent in bvFTD but there are now an increasing number of studies using DTI, rsfMRI, and ASL perfusion MRI.

DTI allows characterization of abnormalities in the structure of white matter fiber tracts in the brain. Diffusion of water is anisotropic (directionally dependent) in these tracts because axons and myelin sheaths act as barriers. Fractional anisotropy (FA) is a measure of the degree of anisotropy of a diffusion process and ranges from zero, when diffusion is isotropic (i.e., unrestricted in all directions), to one, when diffusion occurs only along one axis and is fully restricted in the other directions. FA can therefore provide information on the orientation and integrity of white matter fibers. It is also possible to measure the diffusivity, essentially the rate of diffusion, either as an overall mean within the fibers or in particular directions.

In bvFTD, studies have shown alterations in FA and diffusivity bilaterally in the majority of the frontal white matter tracts including the anterior superior longitudinal fasciculus (SLF), anterior cingulum, and the genu of the corpus callosum, as well as the temporal white matter tracts including the uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF), and inferior fronto-occipital fasciculus (IFOF) [12–14]. Some studies do show changes (albeit to a lesser extent) more posteriorly such as in the posterior cingulate and posterior parts of the SLF, particularly as the disease becomes more severe [15].

rsfMRI examines synchronization of intrinsic fluctuations in blood-oxygen-level-dependent signals arising from neuronal and synaptic activity that is observed independent of overt cognitive information processing.

rsfMRI has been used to elucidate a variety of coherent large-scale functional brain networks, the best described being the default mode network, a set of regions that routinely decrease their activity during attention-demanding tasks. In bvFTD the networks of most interest have been a salience network centered around the ventral frontal cortex, insula, and dorsal anterior cingulate; an executive control network linking dorsolateral frontal and parietal cortices; and also language and semantic networks in the left hemisphere (although these latter networks have been investigated more in primary progressive aphasia [PPA]) [8].

An early rsfMRI study showed that bvFTD is associated with reduced connectivity in the salience network but with increased connectivity in the default mode network (with the opposite pattern being found in Alzheimer's disease [AD]) (Figure 10.4) [16]. This reduced connectivity in the salience network has been replicated in further studies of bvFTD but other results from these studies are conflicting. One study showed similarly increased connectivity in the default mode network [17] whilst others have shown reduced connectivity in the default mode network [18, 19]. It remains unclear why there are such divergent findings in rsfMRI studies in bvFTD, although this may represent differences in the disease stage at which subjects were studied, in the types of underlying pathology represented in the groups, or in the methods used for analysis.

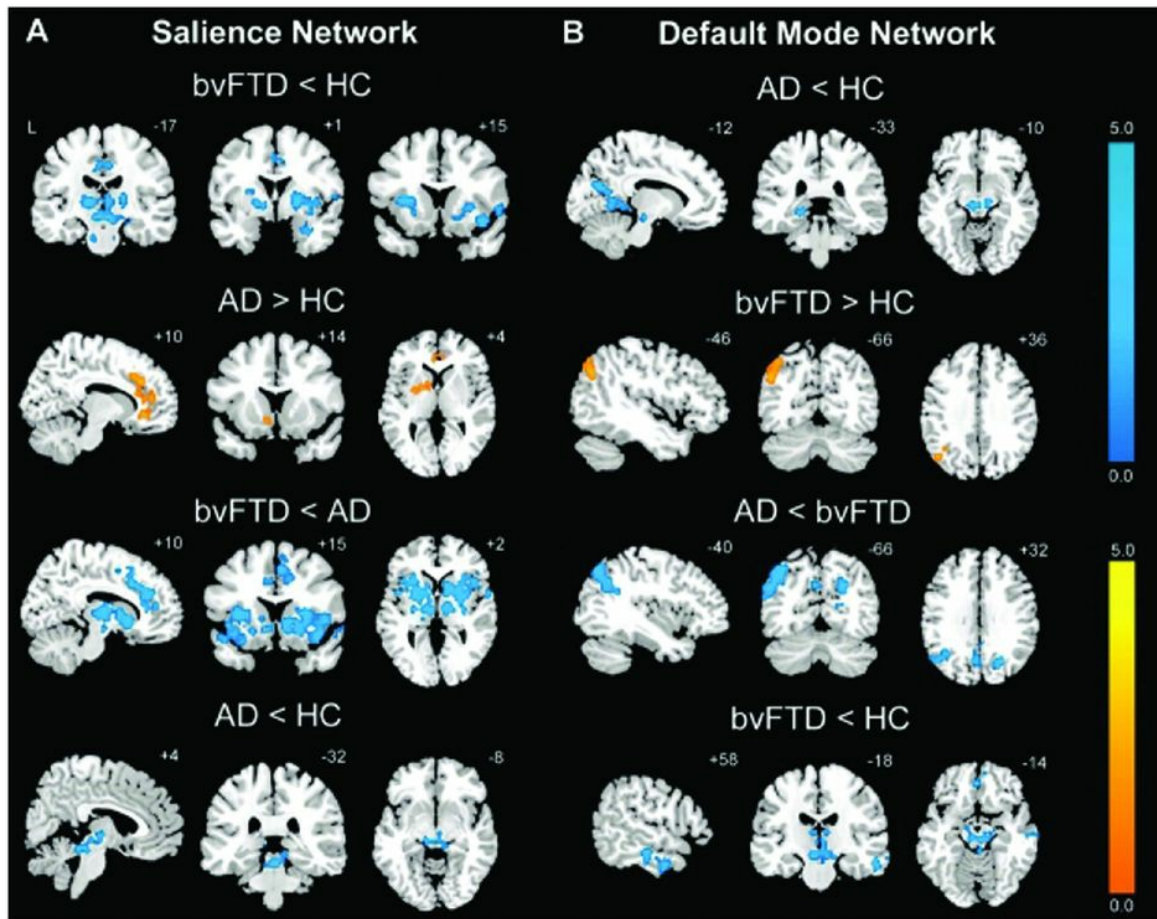


Figure 10.4 An early rsfMRI study showed that bvFTD is associated with reduced connectivity in the salience network (A) but with increased connectivity in the default mode network (B) (with the opposite pattern being found in Alzheimer's disease).

Figure used with permission from Zhou J, Greicius MD, Gennatas ED, *et al.* (2010). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain*, 133(Pt 5), 1352–67.

ASL MRI is a method for assessing brain perfusion (blood flow). Studies in bvFTD have shown hypoperfusion in bilateral frontal regions as well as the anterior cingulate and thalamus compared with controls [20]. A further study looking at a group of patients with FTD that included PPA as well as bvFTD found hypoperfusion compared with controls in dorsolateral prefrontal cortex bilaterally and right inferior fronto-insular areas, with

areas of hyperperfusion in medial parietal cortex, precuneus, and posterior cingulate [21].

Brain perfusion has more commonly been assessed using SPECT and PET by measuring the uptake of a variety of compounds that are labeled with radioactive isotopes. The most commonly studied SPECT method uses ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO), which crosses the blood–brain barrier and is taken up in proportion to blood flow allowing the tracking of cerebral perfusion. The PET compound most commonly used in FTD is [¹⁸F]-fluorodeoxyglucose (FDG), which crosses the blood–brain barrier and is taken up by metabolically active cells thus providing a measure of brain activity.

Both HMPAO-SPECT and FDG-PET have shown a pattern of anterior hypometabolism in the frontal and anterior temporal regions in bvFTD, which similarly to structural T1 imaging may be asymmetric, and may involve subcortical regions [3, 22–25]. A study comparing FTD and AD patients whose diagnoses were ultimately confirmed at autopsy showed that FDG-PET increases diagnostic accuracy beyond clinical features alone [24], with a further study suggesting that FDG-PET combined with structural MRI improves diagnostic accuracy compared with each modality alone [26]. The utility of FDG-PET in diagnosing FTD led to this technique being the first imaging technique approved by the US Medicare health insurance program for diagnosis of FTD (versus AD). Unfortunately, this insurance program is only available to people over 65, and it is often still difficult to obtain insurance reimbursement for FDG-PET in the USA for younger people with private insurance. Similar diagnostic benefits to FDG-PET have been shown for HMPAO-SPECT [23, 25]. There are fewer longitudinal studies of SPECT or PET imaging in bvFTD but one study showed further hypometabolism more posteriorly in the temporal and parietal cortices with disease progression [27].

Newer PET-based imaging techniques have also been used in FTD, particularly those that use ligands that bind to amyloid such as Pittsburgh compound B (PiB). PiB has been demonstrated to differentiate FTD from AD [28], although only small numbers of pathologically verified FTD patients have been studied so far. Of further interest will be ligands that bind to tau protein [29], which are currently under investigation in FTD (see [Chapter 8](#), [Figure 8.4](#)), and those ligands that identify neuroinflammation and microglial activation, processes proposed to be involved in the pathophysiology of FTD [30].

Some patients who present with behavioral symptoms perform normally on neuropsychological tests and do not have abnormalities on structural brain imaging or FDG-PET imaging [31]. These have been termed “bvFTD phenocopies” and do not appear to worsen over time. The majority of these cases remain unexplained but may well not have a neurodegenerative etiology, although some cases have recently been described as having expansions in the *C9orf72* gene.

Frontotemporal dementia with motor neuron disease/amyotrophic lateral sclerosis (FTD-MND/ALS)

As described in detail in [Chapter 6](#), FTD-MND/ALS can present initially with either an FTD syndrome (usually bvFTD, less commonly non-fluent variant of PPA [nfvPPA], and very rarely semantic variant of PPA [svPPA]) or with an MND/ALS syndrome. Early neuroimaging studies of patients with FTD-MND/ALS showed relatively symmetrical frontal and temporal lobe involvement. In a study comparing FTD-MND/ALS with bvFTD without MND/ALS, similar patterns were seen in both groups involving not only the frontal and temporal lobes but also subcortical structures including the thalamus and striatum ([Figure 10.5](#)) [32]. However, there was less

atrophy in the superior frontal lobe and paracingulate gyrus in FTD-MND/ALS compared with bvFTD, with no areas of more atrophy. DTI in this same study showed a similar pattern of involvement of the frontal and temporal white matter tracts in FTD-MND/ALS as in bvFTD but with greater corticospinal tract degeneration (in a pattern similar, although to a lesser extent, to patients with ALS alone). The recognition that many cases of FTD-MND/ALS have expansions in the *C9orf72* gene has allowed better stratification of cases. However, whilst there are now imaging studies comparing pure ALS with and without *C9orf72* expansions, there are no current studies in those with FTD-ALS. Imaging of *C9orf72* expansions are discussed further in the Genetic syndromes section below.

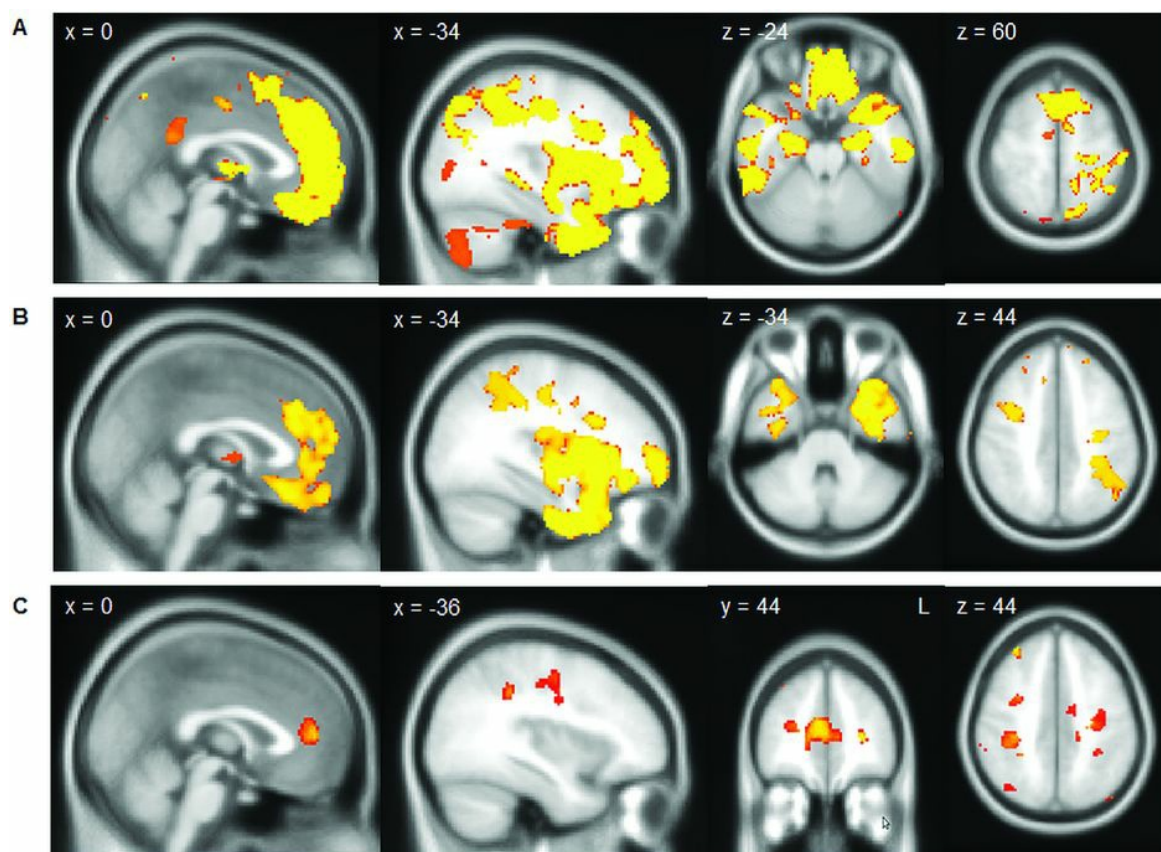


Figure 10.5 In a study comparing FTD-MND/ALS with bvFTD (A, showing areas of greater atrophy in bvFTD than in FTD-MND/ALS) and bvFTD with ALS (B, showing areas of greater atrophy in bvFTD than in ALS without cognitive or behavioral symptoms) similar patterns were seen in both groups

involving not only the frontal and temporal lobes but also subcortical structures including the thalamus and striatum. However, there was less atrophy in the superior frontal lobe and paracingulate gyrus and in the anterior temporal lobe in ALS than in FTD-MND/ALS (C).

Figure used with permission from Lillo P, Mioshi E, Burrell JR, *et al.* (2012). Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. *PLoS One*, 7(8), e43993.

Primary progressive aphasia (PPA)

Semantic variant PPA (svPPA)

svPPA is the most comprehensively studied of the PPA subtypes in terms of cross-sectional patterns of atrophy seen using T1 MRI. Initial VBM studies of clinically diagnosed svPPA identified an asymmetric pattern of atrophy affecting mainly the anterior, inferior, and lateral temporal lobes, more so in the left hemisphere. The findings of these studies were extended by detailed ROI studies of temporal lobe structures, which showed that the temporal pole, fusiform gyrus, entorhinal cortex, inferior temporal gyrus, as well as the amygdala and hippocampus were the most affected areas with relative sparing of the superior temporal gyrus; there was also the presence of an anteroposterior gradient with relative sparing of posterior cortical areas [33]. Further VBM studies showed that there may be involvement of areas outside the temporal lobes in svPPA, particularly orbitofrontal, insular, and anterior cingulate cortices. This asymmetric temporal, frontal, and anterior cingulate pattern distinguishes svPPA from AD, which has more symmetrical hippocampal atrophy involvement without an anteroposterior gradient and greater posterior cingulate and parietal lobe atrophy. Other subcortical regions have also been shown to be involved in svPPA – in a study of caudate, putamen, and nucleus accumbens atrophy, unlike bvFTD

which had panstriatal degeneration, svPPA had more focal involvement of the putamen and nucleus accumbens only [34]. A small VBM study of pathologically confirmed patients found that patterns of atrophy were similar in semantic dementia cases associated with both ubiquitin-positive and tau-positive frontotemporal lobar degeneration (FTLD) pathology but, in the rare cases with Alzheimer's pathology, there was mainly left hippocampal atrophy [35].

The majority of svPPA cases described in the literature have asymmetric left-greater-than-right temporal lobe atrophy, but there are a number of reports of the opposite pattern with right-greater-than-left temporal lobe atrophy. This right temporal variant appears to be less common than the left temporal variant, although this may simply represent an ascertainment bias. Of note, these are different from the rare left-handed/right hemisphere-dominant individuals with svPPA. Patients often have initial behavioral symptoms rather than a progressive aphasia, with the development of semantic impairment only later in the illness (leading some authors to argue that this right temporal variant should be logically separated from the PPAs). In subjects that develop semantic impairment the pattern of atrophy seems to be the mirror image of subjects with left temporal-predominant svPPA and they have the same pathology (i.e., TDP-C) [36]. However, it has been suggested that there is a second right temporal FTD variant that does not develop semantic impairment but has predominantly a bvFTD phenotype – one study showed greater frontal lobe involvement in this group compared with the right temporal svPPA group (with greater fusiform atrophy in the svPPA group) [37].

Longitudinal studies in svPPA are less common. In those with the left temporal variant, there seems to be increased right temporal lobe involvement as the disease progresses, as well as spread of atrophy within the left hemisphere, particularly the more posterior temporal areas and the

orbitofrontal, anterior insular, inferior frontal, and anterior cingulate lobes (Figure 10.6) [38]. In the right temporal variant, limited evidence suggests that a similar but mirror-image pattern of atrophy spread is seen. Rates of whole-brain atrophy in svPPA have been measured in some studies, and these are similar to those seen in other neurodegenerative diseases (1.7–2.5% per year). Rates of individual lobar change are greatest for the temporal lobes (followed by the frontal, parietal, then occipital lobes) [39].

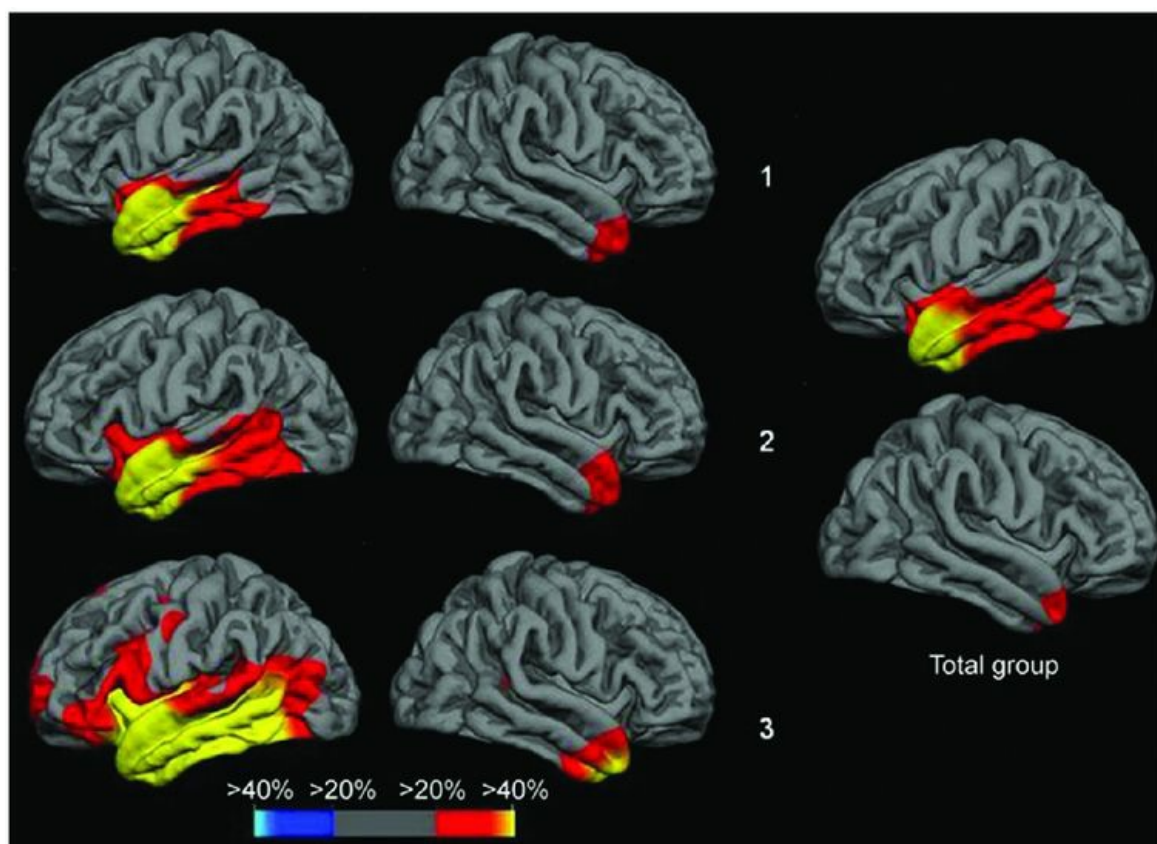


Figure 10.6 Cross-sectional analysis of cortical thickness in svPPA suggests that there is increased right temporal lobe involvement with increasing severity of symptoms, as well as greater atrophy within the left hemisphere, particularly the more posterior temporal areas and the orbitofrontal, anterior insular, inferior frontal, and anterior cingulate lobes. Top row is the subgroup of svPPA patients with the mildest anomia, middle row shows the subgroup with moderate anomia, bottom row shows the subgroup with most severe anomia.

Figure used with permission from Rohrer JD, Warren JD, Modat M, *et al.*

(2009). Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology*, 72(18), 1562–9.

There are now a number of studies investigating the changes in white matter structure in svPPA using DTI [[12](#), [40](#)]. These have shown asymmetric alterations in diffusivity and FA in the ILF and UF with the left side more severely affected. Although some studies have shown relative sparing of the SLF, others that have examined separate parts of the SLF have reported abnormalities in subcomponents, particularly the arcuate fasciculus. Some studies have also shown abnormalities in other tracts including the left IFOF and genu of the corpus callosum.

Asymmetric temporal lobe hypometabolism has been found in PET and SPECT imaging in svPPA but there have been few detailed studies.

Non-fluent variant PPA (nfvPPA)

nfvPPA is less well studied than svPPA, and patterns of neuroanatomical involvement are not quite so clear. This is partly because of the heterogeneity of nfvPPA and also the differences in definition between research groups prior to the recent revision in diagnostic criteria (e.g., it is likely that patients with the logopenic variant PPA [lvPPA] have been included in earlier studies of nfvPPA). Similar to svPPA, atrophy or hypometabolism is usually asymmetric and worse in the left hemisphere. The most significantly affected areas are in the left inferior frontal lobe (particularly the frontal opercular region) and anterior insula [[38](#), [41](#)]. However, left middle and superior frontal, superior temporal, and caudate involvement are also frequently reported in studies, with less frequent involvement of the anterior parietal lobes. ROI studies are limited in nfvPPA, but have shown involvement of striatal structures, particularly the caudate. There are few pathologically confirmed studies of nfvPPA, and

these have often studied mixed pathologic groups but, despite this, have shown fairly consistent findings compared with the clinical studies, e.g., anterior insula and inferior frontal involvement in mixed groups of tau-positive patients [38].

There are few longitudinal studies of nvfPPA, although it seems that, with disease progression, there is spread from the left inferior frontal and insular cortex to involve the superior temporal, middle and superior frontal, and anterior parietal lobes (Figure 10.7) [38]. More posterior atrophy, particularly of the left anterior parietal lobe, may herald the presence of an accompanying corticobasal syndrome (CBS). Rate of whole-brain atrophy is similar to svPPA (1.6% per year) whilst rates of individual lobar change are greatest for the frontal lobes (followed by the temporal/parietal then occipital lobes) [39].

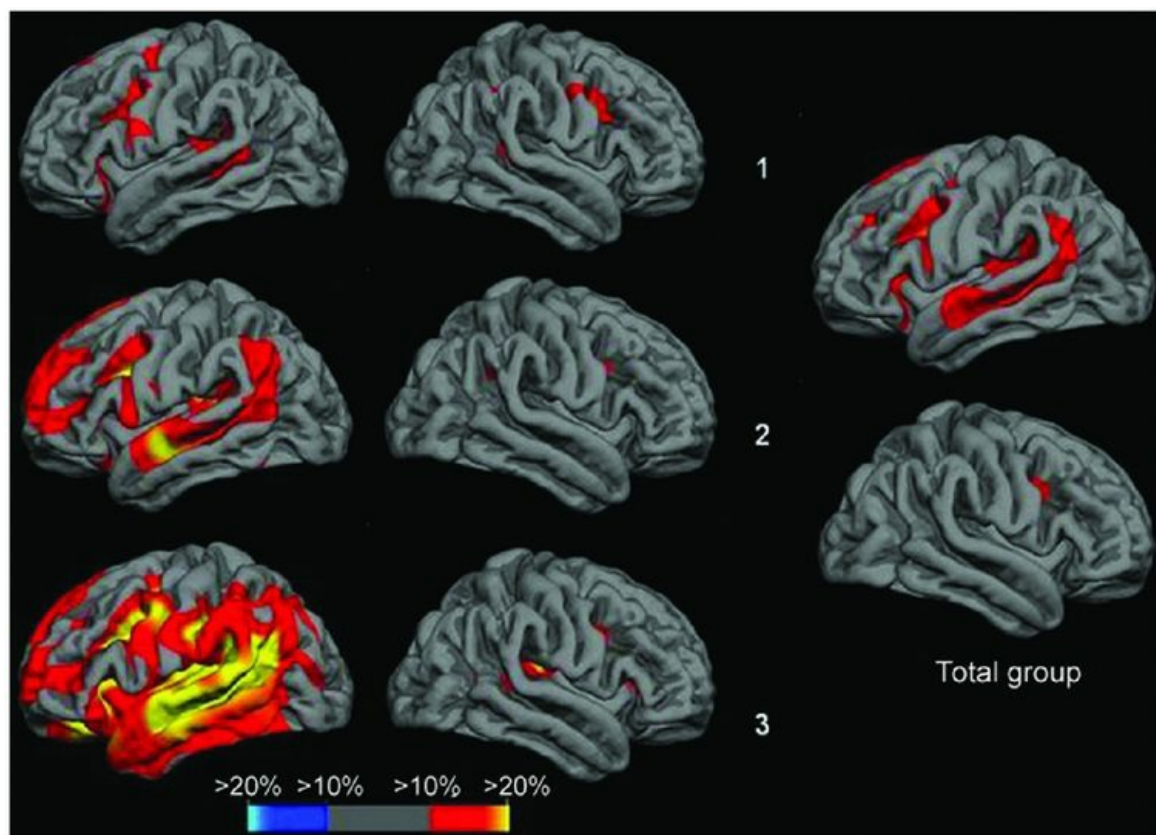


Figure 10.7 Cross-sectional analysis of cortical thickness in nvfPPA suggests that there is increased left inferior frontal and insular involvement with

increasing severity of symptoms, as well as greater atrophy in superior temporal, middle and superior frontal, and anterior parietal lobes. Top row is the subgroup of nfvPPA patients with the mildest anomia, middle row shows the subgroup with moderate anomia, bottom row shows the subgroup with most severe anomia.

Figure used with permission from Rohrer JD, Warren JD, Modat M, *et al.* (2009). Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology*, 72(18), 1562–9.

In contrast to the semantic variant, DTI studies of nfvPPA have shown alterations of diffusivity and FA mostly in the dorsal language pathways, i.e., the subcomponents of the left SLF, particularly the arcuate fasciculus [40]. In patients with predominantly apraxia of speech rather than agrammatism the premotor components of the SLF appear to be affected more than other regions [42]. Other tracts that have shown abnormalities to a lesser extent include the IFOF and UF as well as the fornix and corpus callosum, more so on the left than the right.

Logopenic variant PPA (lvPPA)

lvPPA is the least studied of the three subtypes, with an asymmetric, left-sided predominant pattern of atrophy and hypometabolism affecting the posterior superior temporal and inferior parietal lobes as well as posterior cingulate, precuneus, and middle/inferior temporal lobes ([Figure 10.8](#)) [41, 43]. A longitudinal study of T1 MRI in lvPPA showed a whole-brain atrophy rate of 2.0% per year with a greater rate of left hemisphere atrophy (2.3% per year) than right hemisphere (1.6% per year) [44]. Longitudinal VBM analysis in this study showed spread of atrophy through the left hemisphere (including medial temporal and frontal lobes as well as caudate) and atrophy of areas in the right hemisphere that had been involved

earlier in the disease in the left hemisphere, particularly posterior cingulate/precuneus.

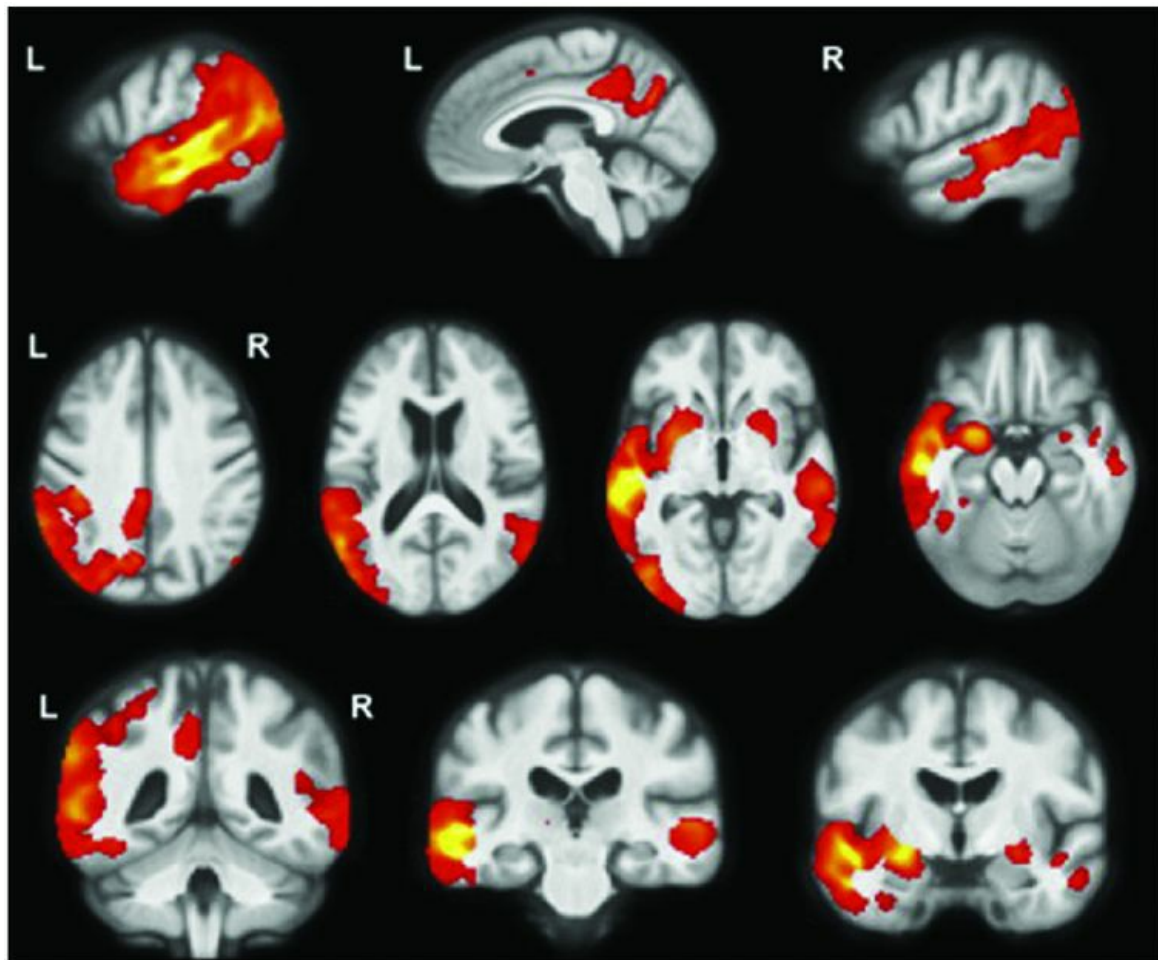


Figure 10.8 lvPPA is the least studied of the three subtypes with an asymmetric, left-sided predominant pattern of atrophy and hypometabolism affecting the posterior superior temporal and inferior parietal lobes as well as posterior cingulate, precuneus, and middle/inferior temporal lobes [41, 43].

Figure used with permission from Rohrer JD, Caso F, Mahoney C, *et al.* (2013). Patterns of longitudinal brain atrophy in the logopenic variant of primary progressive aphasia. *Brain and Language*, 127(2), 121–6.

DTI studies of lvPPA have shown asymmetric, left-sided predominant involvement of tracts including SLF, ILF, and UF [45].

Most studies have found that a majority of cases with lvPPA have underlying AD pathology and hence amyloid imaging with PiB is commonly

positive in a majority of patients in this group.

Other forms of PPA

GRN mutations have been associated with a non-fluent aphasia, although often with a more prominent anomia than other forms of nfvPPA. There are limited studies of the imaging of *GRN*-PPA although these have shown asymmetric left-greater-than-right hemisphere atrophy (which may occur presymptomatically) affecting the frontal, temporal, and (to a lesser extent) parietal lobes. There appears to be more posterior atrophy than usually occurs in nfvPPA (and more anterior temporal lobe atrophy than occurs in lvPPA) [46].

Comparison of bvFTD and the PPA syndromes

Few studies have compared the different FTD clinical syndromes. One study using volumetric imaging and defined ROIs compared bvFTD, svPPA, and nfvPPA [47]: each of the syndromes could be discriminated from each other with relatively high sensitivity and specificity: bvFTD versus svPPA (sensitivity 100%, specificity 100%), bvFTD versus nfvPPA (sensitivity 92%, specificity 89%), and svPPA versus nfvPPA (sensitivity 86%, specificity 100%). svPPA and nfvPPA have also been compared with lvPPA, using an automated structural MRI-based classification method (support vector machines) [48]. As with the first study, discrimination of svPPA from other syndromes had a high specificity (although lower sensitivity) whilst discrimination between the non-svPPA syndromes was not as accurate: svPPA versus nfvPPA (sensitivity 84%, specificity 94%), nfvPPA versus lvPPA (sensitivity 81%, specificity 91%), and svPPA versus lvPPA (sensitivity 94%, specificity 94%).

Genetic syndromes

Studies of genetic FTD have shown different patterns of atrophy associated with the different genes. *MAPT* mutations are associated with relatively symmetrical anterior temporal lobe atrophy with lesser involvement of the orbitofrontal cortices [49, 50]. One small study has shown that there may be differences between patients with *MAPT* mutations that affect splicing (which have more medial temporal lobe involvement) and mutations that affect the structure of the tau protein (which have more lateral temporal lobe involvement). In contrast *GRN* mutations are associated with strongly asymmetric atrophy affecting either the left or right hemispheres maximally and involving the temporal, inferior frontal, and inferior parietal lobes (Figure 10.9) [49, 50]. More recently there have been a number of studies of patients with expansions in the *C9orf72* gene. These have shown relatively symmetrical involvement of the frontal and temporal lobes but also with more posterior cortical involvement, and in contrast to other causes of genetic FTD have shown involvement of the thalamus and cerebellum [50, 51].

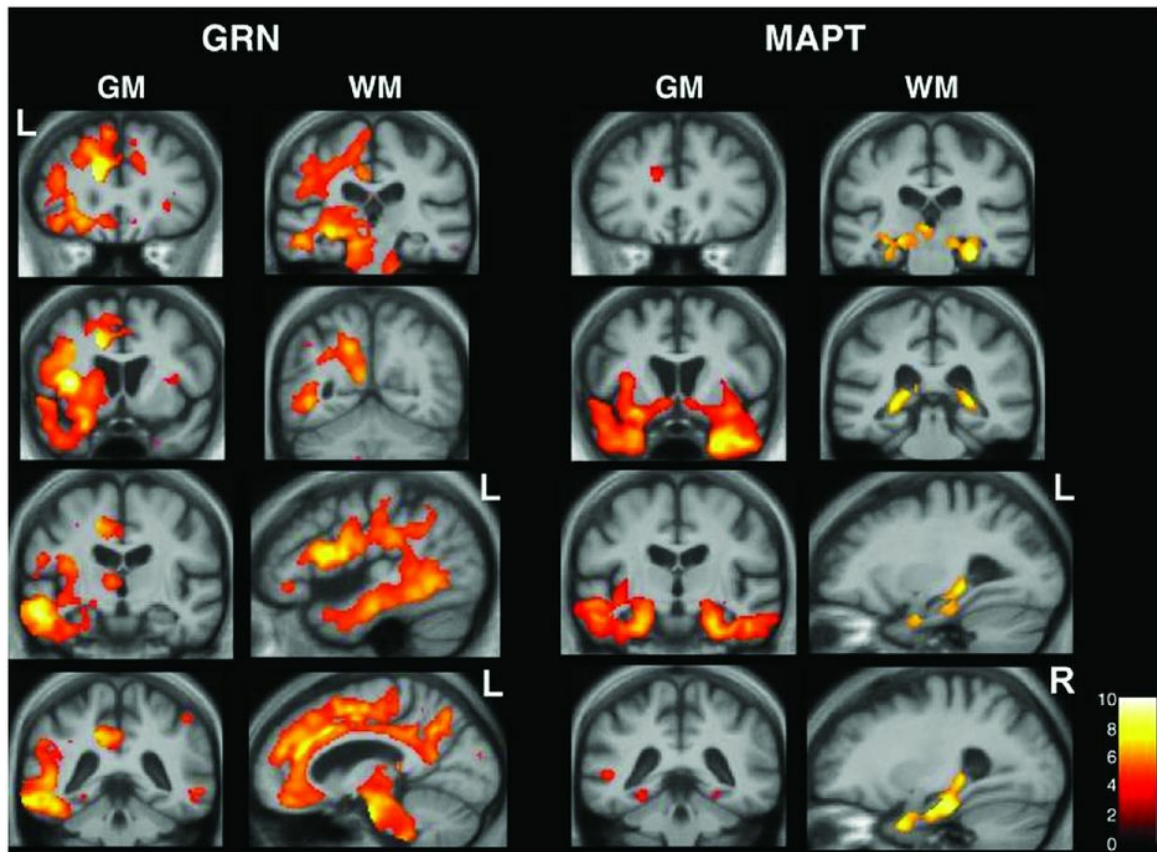


Figure 10.9 Studies of genetic FTD have shown different patterns of atrophy associated with the different genes. *MAPT* mutations are associated with relatively symmetrical anterior temporal lobe atrophy with lesser involvement of the orbitofrontal cortices [49, 50]. One small study has shown that there may be differences between patients with *MAPT* mutations that affect splicing (which have more medial temporal lobe involvement) and mutations that affect the structure of the tau protein (which have more lateral temporal lobe involvement). In contrast *GRN* mutations are associated with strongly asymmetric atrophy affecting either the left or right hemispheres maximally and involving the temporal, inferior frontal, and inferior parietal lobes [49, 50].

Figure used with permission from Rohrer JD, Ridgway GR, Modat M, *et al.* (2010). Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. *Neuroimage*, 53(3), 1070–6.

There are few longitudinal studies of genetic FTD but whole-brain rates of atrophy appear to be greatest for *GRN* (3.4–3.5% per year)

compared with *MAPT* (1.4–2.4% per year) and *C9orf72* mutations (1.4% per year) [50–53].

Studying genetic syndromes offers the opportunity to identify the very earliest imaging features in FTD by investigating presymptomatic patients who are “at risk” of developing FTD. A number of studies have examined presymptomatic genetic FTD although the majority of these have been either individual case reports or relatively small case series so far.

Prior to the manifestation of neuropsychometric abnormalities and several years before disease onset, a number of structural T1 MRI studies have now shown evidence of gray matter atrophy. One study examined a patient with familial FTL-D-U (now known to be associated with a *GRN* mutation) and showed evidence of very focal left frontal lobe atrophy affecting the pars opercularis about two years prior to the onset of nfvPPA. Another single case report of a subject with a *GRN* mutation who later developed nfvPPA showed evidence of early left hemisphere atrophy, particularly in the frontal lobe but also in the middle and inferior temporal gyri and angular gyrus, at least 18 months prior to symptom onset. This was consistent with a study of four presymptomatic *GRN* mutation carriers from a nfvPPA family who had a similar pattern of atrophy and also hypometabolism on FDG-PET scanning [54]. *MAPT* mutations have been studied less frequently, although one study did show presymptomatic hippocampal atrophy [55].

Studies using other imaging modalities have identified presymptomatic changes that appear to occur earlier than gray matter atrophy. A small study of at-risk *GRN* mutation carriers (n = 4) showed no evidence of gray matter atrophy using voxel-based morphometric analysis, but analysis of white matter using DTI showed reduced FA in the left UF and IFOF compared with controls [56]. A larger DTI study of presymptomatic *GRN* mutation carriers (n = 27) also showed decreased FA in the IFOF (on the right) as

well as involvement of the right anterior and superior corona radiata, anterior thalamic radiation, SLF, forceps minor, and internal capsule [57]. In comparison, presymptomatic *MAPT* mutation carriers (n = 9) showed widespread decreased FA (and also increased diffusivity) throughout frontotemporal white matter tracts.

This same study also examined changes in rsfMRI: no changes were seen in *MAPT* mutation carriers but there was reduced connectivity in the anterior midcingulate cortex (an area within the salience network) in *GRN* mutation carriers without any changes in the posterior cingulate cortex (an area within the default mode network) [57]. This is in contrast to another study of presymptomatic *GRN* mutation carriers which showed increased connectivity in a small area in the medial prefrontal cortex (which the authors attribute to the salience network) also without any changes in other networks. Another study of presymptomatic *MAPT* mutation carriers showed reduced connectivity in parts of the default mode network (lateral temporal and medial prefrontal cortices) with increased connectivity in other parts of the default mode network (medial parietal) and no changes in the salience network.

In summary, these studies suggest that there is a sequence of changes seen in different imaging biomarkers of genetic FTD prior to clinical onset of symptoms: the earliest of these markers are likely to be PET imaging with ligands binding to the important FTD proteins (of which tau PET imaging is now available), followed by markers of functional and structural connectivity, then gray matter atrophy, prior to the onset of mild neuropsychometric abnormalities in proximity to the first symptoms. A large cohort study involving multiple centers across Europe and Canada (GENFI, the Genetic FTD Initiative) is currently underway to investigate presymptomatic imaging changes in more detail.

Pathologic syndromes

Initial studies investigating imaging signatures of tau or transactive response DNA-binding protein 43 (TDP-43) pathology did not show a clear picture but with increasing knowledge of the different subtypes of FTD pathology, more recent studies have refined the associations. Two studies of the TDP-43 proteinopathies showed similar findings, with TDP-A pathology being associated with asymmetric fronto-temporo-parietal atrophy, TDP-B with more symmetrical atrophy affecting the frontal lobe but also the insula and anteromedial temporal lobe, and TDP-C showing asymmetric anteroinferior temporal lobe atrophy [[36](#), [58](#)].

Fused in sarcoma (FUS) pathology is relatively rare in FTD but a number of studies have now shown a pattern of atrophy affecting the orbitofrontal lobe, anterior cingulate, insula, anterior temporal lobe, and particularly severely, the caudate [[59](#)].

In the tauopathies, Pick's disease is associated with asymmetric frontal lobe (particularly dorsolateral and orbitofrontal), insular, and anterior temporal lobe atrophy, whilst CBD is associated with less distributed atrophy affecting mostly frontal and to a lesser extent the parietal lobe in a slightly asymmetric pattern [[60](#)].

In pathologically defined FTD, there seem to be more widespread white matter changes seen in the tauopathies on DTI compared to more limited white matter tract involvement in the TDP-43 proteinopathies [[61](#), [62](#)].

Comparison of FTD with other neurodegenerative disorders

Clinically, FTD is usually clearly distinguishable from the typical amnesic AD presentation. However, there can be a gray area with some FTD patients having prominent impairment of episodic memory and some

patients with AD having more atypical presentations, i.e., language variant AD (usually lvPPA), frontal variant AD (i.e., a syndrome with prominent behavioral symptoms and/or executive dysfunction), posterior cortical atrophy (which often presents with visuospatial and/or visuoperceptual impairment and is therefore sometimes called the “visual variant”), and a CBS presentation of AD. In reviewing imaging studies comparing FTD and AD it is therefore important to understand the groups being studied, i.e., whether they are clinical or pathologic phenotypes.

Studies comparing FTD with a typical AD clinical syndrome have shown differences using VBM of structural MRI (atrophy in posterior parietal and occipital cortex in AD compared to atrophy in frontal insula-cingulate and striatum in FTD), cortical thickness (greater parietal and precuneus thinning in AD), amyloid PET imaging (positive in AD), ASL (hypoperfusion in parietal regions and posterior cingulate in AD compared to hypoperfusion in the frontal lobes in FTD), DTI (reduced FA in frontal brain regions in FTD), and as described above, both HMPAO-SPECT and FDG-PET. Automated methods of classification using support vector machines have shown the ability to accurately differentiate AD and FTD with relatively high sensitivity and specificity.

Studies investigating more atypical phenotypes of AD have suggested that, independent of clinical phenotype, patients with underlying AD pathology have involvement of posterior cingulate, precuneus, posterior parietal, and medial temporal areas. Comparison of PPA patients with and without AD pathology suggests that differentiating factors between these two groups include greater left temporo-parietal atrophy in those with AD pathology (usually an lvPPA syndrome clinically) and the presence of knife-edge anterior temporal lobe atrophy in those with FTD pathology.

Less commonly, FTD can be mistaken for dementia with Lewy bodies (DLB) – this may well be because some patients with FTD clinical

syndromes can develop delusions and/or visual hallucinations. One small study suggested that MRI was not helpful in differentiating FTD from DLB. Furthermore, ^{123}I -FP-CIT SPECT scans (DaTscans) can be abnormal in FTD (in a third of patients in one recent small study). However a further study has shown accurate differentiation using ^{123}I -MIBG scintigraphy in which uptake is markedly reduced in DLB but normal in FTD.

Brain–behavior correlation

Imaging studies in FTD have not only looked at patterns of MRI, SPECT, and PET changes relative to disease state but also in relation to the underlying symptomatology.

Behavioral variant FTD

Patients with bvFTD tend to have one or more behavioral symptoms which in the recent diagnostic criteria have been grouped into five domains: apathy and loss of motivation, disinhibition and socially inappropriate behavior, loss of empathy or sympathy for others, change in eating behavior including the development of a sweet tooth, and repetitive or obsessive–compulsive behavior. Apathy has been associated with atrophy in a variety of areas including the prefrontal cortex, temporal lobe, caudate, anterior cingulate, and insula [[63](#), [64](#)], whilst disinhibition has been associated with the orbitofrontal cortex as well as the anterior temporal lobe [[64](#), [65](#)]. A DTI study of disinhibition showed association with UF, forceps minor, and genu of the corpus callosum [[65](#)]. Empathy has also been associated with prefrontal and anterior temporal lobe atrophy [[66](#)]. Abnormal eating behavior was found to be associated with orbitofrontal cortex and right insular atrophy [[67](#), [68](#)] although a recent study has looked at the

involvement of the hypothalamus [69]. Lastly, obsessive–compulsive behavior has been associated with atrophy bilaterally in the globus pallidus as well as the left putamen and lateral temporal lobe [70]. Patients often do not have insight into their behavioral deficits, and one study has shown an association between the degree of anosognosia and atrophy in the right superior temporal lobe [71].

Cognitively, patients with bvFTD tend to have executive dysfunction and impaired social cognition most prominently but may develop impairment in other cognitive domains including episodic memory. Executive dysfunction and social cognition have both been associated with atrophy of the prefrontal cortex although a task of sarcasm detection was associated with atrophy in the orbitofrontal cortex, insula, amygdala, and temporal pole, particularly on the right [72]. A recent study has shown distinct anatomical correlates of episodic memory between patients with bvFTD and AD with ventromedial and dorsolateral prefrontal cortex contributions in bvFTD but only dorsolateral prefrontal cortex involvement in AD.

Primary progressive aphasia

Patients with PPA have a wide variety of speech and language deficits that differ between the subtypes: anomia and impaired single-word comprehension secondary to a verbal semantic deficit in svPPA; agrammatism, motor speech impairment, anomia, and impaired repetition in nfvPPA; and anomia and impaired sentence repetition and comprehension secondary to a phonologic memory deficit in lvPPA. Consistent with this, both structural and functional MRI studies have shown involvement of a distributed left hemisphere fronto-temporo-parietal language network in PPA. During the early stages of the disease, all of the disorders have naming

deficits with anomia worse in svPPA than lvPPA and only a mild impairment in nfvPPA. VBM studies suggest that overlapping but distinct areas of the language network correlate with anomia: in svPPA, anomia is mostly associated with anterior temporal lobe atrophy, whereas in nfvPPA, a more widespread network of areas is associated with anomia, particularly the inferior frontal, lateral temporal, and anterior parietal lobes. More recently, DTI studies have looked at the white matter tract correlates of naming and have again found distinct findings between the subtypes, e.g., an association with left UF and corpus callosum in svPPA and left superior and inferior longitudinal fasciculi in lvPPA [73].

There are few studies of spontaneous speech in PPA, and those performed have looked mainly at nfvPPA: apraxia of speech has been associated with premotor and supplementary motor areas as well as the insula and basal ganglia, whereas early mutism in nfvPPA has been associated with left pars opercularis and basal ganglia atrophy. In a study looking at the three variants, motor speech and syntax deficits were associated with frontal lobe atrophy whilst lexical retrieval was associated with inferior temporal lobe atrophy and the presence of phonologic errors was associated with posterior temporal lobe atrophy [74]. Sentence comprehension is impaired in both nfvPPA (for complex sentences) and lvPPA (for simple and complex sentences) with one small fMRI study of nfvPPA showing decreased activation in the left ventral inferior frontal lobe areas known to be associated with grammatical processing. Reading deficits differ between the subtypes: surface dyslexia is seen in svPPA (i.e., inability to read irregular or exception words) and, in an fMRI study, a group of svPPA patients (unlike cognitively normal control subjects) did not activate anterior temporal lobe areas thought to be required for exception word reading, but instead activated a left inferior parietal area not seen in normal individuals (which may explain the regularization of exception

words that svPPA patients commonly exhibit). Phonologic dyslexia is seen in nvPPA and lvPPA, i.e., particular difficulty reading nonsense or pseudowords, and is associated in PPA with left temporo-parietal atrophy.

Non-linguistic deficits are also seen in PPA as the disease progresses. Executive dysfunction is seen in nvPPA, and patients have been included in correlative studies linking such deficits with prefrontal atrophy. Prosopagnosia develops in svPPA with greater right temporal lobe involvement, while emotional processing deficits are also associated with right hemisphere atrophy, namely in the amygdala and orbitofrontal cortex. Behavioral deficits in PPA are associated with orbitofrontal lobe atrophy as well as right dorsolateral prefrontal cortex (apathy) and left anterior temporal lobe (disinhibition) [[75](#)].

References

1. Knopman DS, Christensen KJ, Schut LJ, Harbaugh RE, Reeder T, Ngo T, Frey W 2nd. The spectrum of imaging and neuropsychological findings in Pick's disease. *Neurology* 1989;**39**(3):362–8.
2. Frisoni GB, Beltramello A, Geroldi C, Weiss C, Bianchetti A, Trabucchi M. Brain atrophy in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 1996;**61**(2):157–65.
3. Miller BL, Gearhart R. Neuroimaging in the diagnosis of frontotemporal dementia. *Dement Geriatr Cogn Disord* 1999;**10**(Suppl 1):71–4.
4. Schroeter ML, Raczka K, Neumann J, Yves von Cramon D. Towards a nosology for frontotemporal lobar degenerations-a meta-analysis involving 267 subjects. *Neuroimage* 2007;**36**(3):497–510.
5. Schroeter ML, Raczka K, Neumann J, von Cramon DY. Neural networks in

frontotemporal dementia – a meta-analysis. *Neurobiol Aging* 2008;**29**(3):418–26.

6. Seeley WW, Crawford R, Rascofsky K, Kramer JH, Weiner M, Miller BL, Gorno-Tempini ML. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol* 2008;**65**(2):249–55.

7. Whitwell JL, Jack CR Jr, Senjem ML, Parisi JE, Boeve BF, Knopman DS, Dickson DW, Petersen RC, Josephs KA. MRI correlates of protein deposition and disease severity in postmortem frontotemporal lobar degeneration. *Neurodegener Dis* 2009;**6**(3):106–17.

8. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron* 2009;**62**(1):42–52.

9. Whitwell JL, Przybelski SA, Weigand SD, Ivnik RJ, Vemuri P, Gunter JL, Senjem ML, Shiung MM, Boeve BF, Knopman DS, Parisi JE, Dickson DW, Petersen RC, Jack CR Jr, Josephs KA. Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study. *Brain* 2009;**132**(Pt 11):2932–46.

10. Knopman DS, Jack CR Jr, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo ND. Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year. *Neurology* 2009;**72**(21):1843–9.

11. Gordon E, Rohrer JD, Kim LG, Omar R, Rossor MN, Fox NC, Warren JD. Measuring disease progression in frontotemporal lobar degeneration: a clinical and MRI study. *Neurology* 2010;**74**(8):666–73.

12. Borroni B, Brambati SM, Agosti C, Gipponi S, Bellelli G, Gasparotti R, Garibotto V, Di Luca M, Scifo P, Perani D, Padovani A. Evidence of white matter changes on diffusion tensor imaging in frontotemporal dementia. *Arch Neurol* 2007;**64**(2):246–51.

-
- 13.** Zhang Y, Schuff N, Du AT, Rosen HJ, Kramer JH, Gorno-Tempini ML, Miller BL, Weiner MW. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain* 2009;**132**(Pt 9):2579–92.
-
- 14.** Whitwell JL, Avula R, Senjem ML, Kantarci K, Weigand SD, Samikoglu A, Edmonson HA, Vemuri P, Knopman DS, Boeve BF, Petersen RC, Josephs KA, Jack CR Jr. Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia. *Neurology* 2010;**74**(16):1279–87.
-
- 15.** Mahoney CJ, Ridgway GR, Malone IB, Downey LE, Beck J, Kinnunen KM, Schmitz N, Golden HL, Rohrer JD, Schott JM, Rossor MN, Ourselin S, Mead S, Fox NC, Warren JD. Profiles of white matter tract pathology in frontotemporal dementia. *Hum Brain Mapp* 2014;**35**(8):163–79.
-
- 16.** Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, Kramer JH, Weiner M, Miller BL, Seeley WW. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain* 2010;**133**(Pt 5):1352–67.
-
- 17.** Farb NA, Grady CL, Strother S, Tang-Wai DF, Masellis M, Black S, Freedman M, Pollock BG, Campbell KL, Hasher L, Chow TW. Abnormal network connectivity in frontotemporal dementia: evidence for prefrontal isolation. *Cortex* 2013;**49**(7):1856–73.
-
- 18.** Whitwell JL, Josephs KA, Avula R, Tosakulwong N, Weigand SD, Senjem ML, Vemuri P, Jones DT, Gunter JL, Baker M, Wszolek ZK, Knopman DS, Rademakers R, Petersen RC, Boeve BF, Jack CR Jr. Altered functional connectivity in asymptomatic MAPT subjects: a comparison to bvFTD. *Neurology* 2011;**77**(9):866–74.
-
- 19.** Filippi M, Agosta F, Scola E, Canu E, Magnani G, Marcone A, Valsasina P, Caso F, Copetti M, Comi G, Cappa SF, Falini A. Functional network connectivity in the behavioral variant of frontotemporal dementia. *Cortex* 2013;**49**(9):2389–401.

-
- 20.** Du AT, Jahng GH, Hayasaka S, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin KP, Miller BL, Weiner MW, Schuff N. Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI. *Neurology* 2006;**67**(7):1215–20.
-
- 21.** Hu WT, Wang Z, Lee VM, Trojanowski JQ, Detre JA, Grossman M. Distinct cerebral perfusion patterns in FTLT and AD. *Neurology* 2010;**75**(10):881–8.
-
- 22.** McMurtray AM, Chen AK, Shapira JS, Chow TW, Mishkin F, Miller BL, Mendez MF. Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. *Neurology* 2006;**66**(4):517–22.
-
- 23.** McNeill R, Sare GM, Manoharan M, Testa HJ, Mann DM, Neary D, Snowden JS, Varma AR. Accuracy of single-photon emission computed tomography in differentiating frontotemporal dementia from Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2007;**78**(4):350–5.
-
- 24.** Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, DeCarli CS, Turner RS, Koeppe RA, Higdon R, Minoshima S. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain* 2007;**130**(Pt 10):2616–35.
-
- 25.** Rollin-Sillaire A, Bombois S, Deramecourt V, Steinert-Emptaz A, Salleron J, Morvan J, Maurage CA, Steinling M, Pasquier F. Contribution of single photon emission computed tomography to the differential diagnosis of dementia in a memory clinic. *J Alzheimers Dis* 2012;**30**(4):833–45.
-
- 26.** Dukart J, Mueller K, Horstmann A, Barthel H, Möller HE, Villringer A, Sabri O, Schroeter ML. Combined evaluation of FDG-PET and MRI improves detection and differentiation of dementia. *PLoS One* 2011;**6**(3):e18111.
-
- 27.** Diehl-Schmid J, Grimmer T, Drzezga A, Bornschein S, Riemenschneider M, Förstl H, Schwaiger M, Kurz A. Decline of cerebral glucose metabolism in

frontotemporal dementia: a longitudinal 18F-FDG-PET-study. *Neurobiol Aging* 2007;**28**(1):42–50.

28. Rabinovici GD, Furst AJ, O'Neil JP, Racine CA, Mormino EC, Baker SL, Chetty S, Patel P, Pagliaro TA, Klunk WE, Mathis CA, Rosen HJ, Miller BL, Jagust WJ. 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology* 2007;**68**(15):1205–12.

29. Chien DT, Bahri S, Szardenings AK, Walsh JC, Mu F, Su MY, Shankle WR, Elizarov A, Kolb HC. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J Alzheimers Dis* 2013;**34**(2):457–68.

30. Cagnin A, Rossor M, Sampson EL, Mackinnon T, Banati RB. In vivo detection of microglial activation in frontotemporal dementia. *Ann Neurol* 2004;**56**(6):894–7.

31. Kipps CM, Hodges JR, Fryer TD, Nestor PJ. Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype. *Brain* 2009;**132**(Pt 9):2566–78.

32. Lillo P, Mioshi E, Burrell JR, Kiernan MC, Hodges JR, Hornberger M. Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. *PLoS One* 2012;**7**(8):e43993.

33. Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, Rossor AM, Stevens JM, Ciolotti L, Rossor MN. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol* 2001;**49**(4):433–42.

34. Halabi C, Halabi A, Dean DL, Wang PN, Boxer AL, Trojanowski JQ, Dearmond SJ, Miller BL, Kramer JH, Seeley WW. Patterns of striatal degeneration in frontotemporal dementia. *Alzheimer Dis Assoc Disord* 2013;**27**(1):74–83.

35. Pereira JM, Williams GB, Acosta-Cabronero J, Pengas G, Spillantini MG,

Xuereb JH, Hodges JR, Nestor PJ. Atrophy patterns in histologic vs clinical groupings of frontotemporal lobar degeneration. *Neurology* 2009;**72**(19):1653–60.

36. Rohrer JD, Geser F, Zhou J, Gennatas ED, Sidhu M, Trojanowski JQ, Dearmond SJ, Miller BL, Seeley WW. TDP-43 subtypes are associated with distinct atrophy patterns in frontotemporal dementia. *Neurology* 2010;**75**(24):2204–11.

37. Josephs KA, Whitwell JL, Knopman DS, Boeve BF, Vemuri P, Senjem ML, Parisi JE, Ivnik RJ, Dickson DW, Petersen RC, Jack CR Jr. Two distinct subtypes of right temporal variant frontotemporal dementia. *Neurology* 2009;**73**(18):1443–50.

38. Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, Rossor MN, Ourselin S, Fox NC. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology* 2009;**72**(18):1562–9.

39. Rohrer JD, Clarkson MJ, Kittus R, Rossor MN, Ourselin S, Warren JD, Fox NC. Rates of hemispheric and lobar atrophy in the language variants of frontotemporal lobar degeneration. *J Alzheimers Dis* 2012;**30**(2):407–11.

40. Agosta F, Henry RG, Migliaccio R, Neuhaus J, Miller BL, Dronkers NF, Brambati SM, Filippi M, Ogar JM, Wilson SM, Gorno-Tempini ML. Language networks in semantic dementia. *Brain* 2010;**133**(Pt 1):286–99.

41. Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, Johnson JK, Weiner MW, Miller BL. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol* 2004;**55**(3):335–46.

42. Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Master AV, Lowe VJ, Jack CR Jr, Whitwell JL. Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. *Brain* 2012;**135**(Pt 5):1522–36.

43. Madhavan A, Whitwell JL, Weigand SD, Duffy JR, Strand EA, Machulda MM, Tosakulwong N, Senjem ML, Gunter JL, Lowe VJ, Petersen RC, Jack CR Jr, Josephs KA. FDG PET and MRI in logopenic primary progressive aphasia versus dementia of the Alzheimer's type. *PLoS One* 2013;**8**(4):e62471.

44. Rohrer JD, Caso F, Mahoney C, Henry M, Rosen HJ, Rabinovici G, Rossor MN, Miller B, Warren JD, Fox NC, Ridgway GR, Gorno-Tempini ML. Patterns of longitudinal brain atrophy in the logopenic variant of primary progressive aphasia. *Brain Lang* 2013;**127**(2):121–6.

45. Mahoney CJ, Malone IB, Ridgway GR, Buckley AH, Downey LE, Golden HL, Ryan NS, Ourselin S, Schott JM, Rossor MN, Fox NC, Warren JD. White matter tract signatures of the progressive aphasia. *Neurobiol Aging* 2013;**34**(6):1687–99.

46. Rohrer JD, Ridgway GR, Crutch SJ, Hailstone J, Goll JC, Clarkson MJ, Mead S, Beck J, Mummery C, Ourselin S, Warrington EK, Rossor MN, Warren JD. Progressive logopenic/phonological aphasia: erosion of the language network. *Neuroimage* 2010;**49**(1):984–93.

47. Lindberg O, Ostberg P, Zandbelt BB, Oberg J, Zhang Y, Andersen C, Looi JC, Bogdanović N, Wahlund LO. Cortical morphometric subclassification of frontotemporal lobar degeneration. *AJNR Am J Neuroradiol* 2009;**30**(6):1233–9.

48. Wilson SM, Ogar JM, Laluz V, Growdon M, Jang J, Glenn S, Miller BL, Weiner MW, Gorno-Tempini ML. Automated MRI-based classification of primary progressive aphasia variants. *Neuroimage* 2009;**47**(4):1558–67.

49. Rohrer JD, Ridgway GR, Modat M, Ourselin S, Mead S, Fox NC, Rossor MN, Warren JD. Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. *Neuroimage* 2010;**53**(3):1070–6.

50. Whitwell JL, Weigand SD, Boeve BF, Senjem ML, Gunter JL, DeJesus-

Hernandez M, Rutherford NJ, Baker M, Knopman DS, Wszolek ZK, Parisi JE, Dickson DW, Petersen RC, Rademakers R, Jack CR Jr, Josephs KA.

Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. *Brain* 2012;**135**(Pt 3):794–806.

51. Mahoney CJ, Beck J, Rohrer JD, Lashley T, Mok K, Shakespeare T, Yeatman T, Warrington EK, Schott JM, Fox NC, Rossor MN, Hardy J, Collinge J, Revesz T, Mead S, Warren JD. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. *Brain* 2012;**135**(Pt 3):736–50.

52. Mahoney CJ, Downey LE, Ridgway GR, Beck J, Clegg S, Blair M, Finnegan S, Leung KK, Yeatman T, Golden H, Mead S, Rohrer JD, Fox NC, Warren JD. Longitudinal neuroimaging and neuropsychological profiles of frontotemporal dementia with C9ORF72 expansions. *Alzheimers Res Ther* 2012;**4**(5):41.

53. Whitwell JL, Weigand SD, Gunter JL, Boeve BF, Rademakers R, Baker M, Knopman DS, Wszolek ZK, Petersen RC, Jack CR Jr, Josephs KA. Trajectories of brain and hippocampal atrophy in FTD with mutations in MAPT or GRN. *Neurology* 2011;**77**(4):393–8.

54. Cruchaga C, Fernández-Seara MA, Seijo-Martínez M, Samaranch L, Lorenzo E, Hinrichs A, Irigoyen J, Maestro C, Prieto E, Martí-Clement JM, Arbizu J, Pastor MA, Pastor P. Cortical atrophy and language network reorganization associated with a novel progranulin mutation. *Cereb Cortex* 2009;**19**(8):1751–60.

55. Miyoshi M, Shinotoh H, Wszolek ZK, Strongosky AJ, Shimada H, Arakawa R, Higuchi M, Ikoma Y, Yasuno F, Fukushima K, Irie T, Ito H, Suhara T. In vivo detection of neuropathologic changes in presymptomatic MAPT mutation carriers: a PET and MRI study. *Parkinsonism Relat Disord* 2010;**16**(6):404–8.

56. Borroni B, Alberici A, Premi E, Archetti S, Garibotto V, Agosti C,

Gasparotti R, Di Luca M, Perani D, Padovani A. Brain magnetic resonance imaging structural changes in a pedigree of asymptomatic progranulin mutation carriers. *Rejuvenation Res* 2008;**11**(3):585–95.

57. Doppert EG, Rombouts SA, Jiskoot LC, Heijer TD, de Graaf JR, Koning ID, Hammerslag AR, Seelaar H, Seeley WW, Veer IM, van Buchem MA, Rizzu P, van Swieten JC. Structural and functional brain connectivity in presymptomatic familial frontotemporal dementia. *Neurology* 2013;**80**(9):814–23.

58. Whitwell JL, Jack CR Jr, Parisi JE, Senjem ML, Knopman DS, Boeve BF, Rademakers R, Baker M, Petersen RC, Dickson DW, Josephs KA. Does TDP-43 type confer a distinct pattern of atrophy in frontotemporal lobar degeneration? *Neurology* 2010;**75**(24):2212–20.

59. Lee SE, Seeley WW, Poorzand P, Rademakers R, Karydas A, Stanley CM, Miller BL, Rankin KP. Clinical characterization of bvFTD due to FUS neuropathology. *Neurocase* 2012;**18**(4):305–17.

60. Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, Beck J, Hardy J, de Silva R, Warrington E, Troakes C, Al-Sarraj S, King A, Borroni B, Clarkson MJ, Ourselin S, Holton JL, Fox NC, Revesz T, Rossor MN, Warren JD. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain* 2011;**134**(Pt 9):2565–81.

61. McMillan CT, Irwin DJ, Avants BB, Powers J, Cook PA, Toledo JB, McCarty Wood E, Van Deerlin VM, Lee VM, Trojanowski JQ, Grossman M. White matter imaging helps dissociate tau from TDP-43 in frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2013;**84**(9):949–55.

62. Sajjadi SA, Acosta-Cabronero J, Patterson K, Diaz-de-Grenu LZ, Williams GB, Nestor PJ. Diffusion tensor magnetic resonance imaging for single subject diagnosis in neurodegenerative diseases. *Brain* 2013;**136**(Pt 7):2253–61.

63. Eslinger PJ, Moore P, Antani S, Anderson C, Grossman M. Apathy in frontotemporal dementia: behavioral and neuroimaging correlates. *Behav Neurol* 2012;**25**(2):127–36.

64. Zamboni G, Huey ED, Krueger F, Nichelli PF, Grafman J. Apathy and disinhibition in frontotemporal dementia: insights into their neural correlates. *Neurology* 2008;**71**(10):736–42.

65. Hornberger M, Geng J, Hodges JR. Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia. *Brain* 2011;**134**(Pt 9):2502–12.

66. Eslinger PJ, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. *J Neuropsychiatry Clin Neurosci* 2011;**23**(1):74–82.

67. Woolley JD, Gorno-Tempini ML, Seeley WW, Rankin K, Lee SS, Matthews BR, Miller BL. Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. *Neurology* 2007;**69**(14):1424–33.

68. Whitwell JL, Sampson EL, Loy CT, Warren JE, Rossor MN, Fox NC, Warren JD. VBM signatures of abnormal eating behaviours in frontotemporal lobar degeneration. *Neuroimage* 2007;**35**(1):207–13.

69. Piguet O, Petersén A, Yin Ka Lam B, Gabery S, Murphy K, Hodges JR, Halliday GM. Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. *Ann Neurol* 2011;**69**(2):312–19.

70. Perry DC, Whitwell JL, Boeve BF, Pankratz VS, Knopman DS, Petersen RC, Jack CR Jr, Josephs KA. Voxel-based morphometry in patients with obsessive-compulsive behaviors in behavioral variant frontotemporal dementia. *Eur J Neurol* 2012;**19**(6):911–17.

71. Zamboni G, Grafman J, Krueger F, Knutson KM, Huey ED. Anosognosia

for behavioral disturbances in frontotemporal dementia and corticobasal syndrome: a voxel-based morphometry study. *Dement Geriatr Cogn Disord* 2010;**29**(1):88–96.

72. Kipps CM, Nestor PJ, Acosta-Cabronero J, Arnold R, Hodges JR. Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing. *Brain* 2009;**132**(Pt 3):592–603.

73. Powers JP, McMillan CT, Brun CC, Yushkevich PA, Zhang H, Gee JC, Grossman M. White matter disease correlates with lexical retrieval deficits in primary progressive aphasia. *Front Neurol* 2013;**4**:212.

74. Wilson SM, Henry ML, Besbris M, Ogar JM, Dronkers NF, Jarrold W, Miller BL, Gorno-Tempini ML. Connected speech production in three variants of primary progressive aphasia. *Brain* 2010;**133**(Pt 7):2069–88.

75. Rohrer JD, Warren JD. Phenomenology and anatomy of abnormal behaviours in primary progressive aphasia. *J Neurol Sci* 2010;**293**(1–2):35–8.

Chapter 11

Cerebrospinal fluid biomarkers of frontotemporal lobar degeneration



Nicolaas A. Verwey, Yolande A. L. Pijnenburg, and Philip Scheltens

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Accurate ante-mortem diagnosis in frontotemporal lobar degeneration (FTLD) is essential for establishing a clinical prognosis and tailoring patient management. Moreover, in the light of potential future therapies, biomarkers discerning the underlying FTLD subtype as well as monitoring treatment response are indispensable. Till now, there is no specific biochemical marker for diagnosis of FTLD or one of its subtypes, nor for predicting the course of this disease. However, there is light at the end of the tunnel. Cerebrospinal fluid (CSF) tau, P-tau, and amyloid- β 42 (A β 42) are well-established CSF biomarkers that can be helpful in the diagnosis of FTLD by excluding Alzheimer's disease. In addition, new approaches have been set in the last few years to discover new biomarkers, not only to certify FTLD, but also to differentiate between the different neuropathologic forms

of FTLD. In this chapter we will give an outline of the CSF biomarkers that have been studied in FTLD till now.

Introduction

Cerebrospinal fluid (CSF) biomarkers may be of great use in establishing an accurate diagnosis of frontotemporal lobar degeneration (FTLD) or one of its subtypes. CSF protein composition is considered to reflect the pathologic processes taking place in the brain, and is therefore an ideal testing platform. Additionally, CSF is easily accessible, making it very useful for diagnostic purposes.

FTLD is a spectrum of disorders with similar clinical presentations, based on different underlying neuropathologic processes. As described in detail in [Chapter 13](#), three main neuropathologic subgroups can be discerned [[1–3](#)]. The most common neuropathologic abnormality is FTLD-TDP in which accumulation of ubiquitinated and hyperphosphorylated transactive DNA-binding protein of approximately 43 kDa (TDP-43) is found in brain tissue. FTLD-tau is another subtype characterized by accumulation of the microtubule-associated tau protein. The last and rarest form is FTLD-FUS, which is related histopathologically to fused in sarcoma (FUS) immune-reactive inclusions [[4](#)].

The ideal CSF biomarker in FTLD has to be highly sensitive and specific and apart from having a significant additional value over the clinical diagnosis, it should reflect neuropathologic processes and help to distinguish between the different pathologic forms of FTLD [[5](#)].

In Alzheimer's disease (AD), CSF tau, P-tau (phosphorylated tau), and amyloid- β 42 (A β 42) have been well validated as CSF biomarkers. Additionally, a substantial number of papers have been published using

these biomarkers in clinical dementia differential diagnosis. Motivated in part by that success, we have seen substantial research performed on CSF biomarkers in FTLD [[6–15](#)].

This chapter will outline the CSF biomarkers that have been investigated in FTLD so far. Hypothesis-driven approaches have been applied in studies investigating CSF levels of proteins involved in pathology or genetics of FTLD. Non-hypothesis-driven approaches have been used in technically sophisticated quests for differences between FTLD CSF protein patterns and other dementias and controls.

Hypothesis-driven CSF research in FTLD

Progranulin and TDP-43 in CSF of FTLD patients

The most common pathologic abnormality in FTLD-TDP is accumulation of ubiquitinated and hyperphosphorylated TDP-43 in brain tissue. This pathologic hallmark occurs in genetically sporadic cases and has also been associated with progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9orf72*) genetic mutations (see [Chapter 14](#) for details on the genetics of FTLD). Pathogenic mutations in the *GRN* gene are of various types and result in substantially reduced levels of progranulin (PGRN) in body fluids [[16](#)]. As a consequence, the most logical approach is to measure PGRN and TDP-43 in CSF. Nevertheless, the number of publications addressing this subject is still limited.

PGRN is a 593-amino acid secreted glycoprotein composed of a signal peptide followed by 7.5 tandem repeats of a 12-cysteinyll granulin motif that can be proteolytically cleaved to form a family of 6-kDa granulin peptides (GRN). Both PGRN and GRN peptides are believed to play a key role in

cell cycle progression/development, cell motility, neuritic outgrowth, wound repair, and inflammation [17].

Current knowledge suggests that PGRN deficiency increases factors leading to cellular stress, and in combination with other disease modulators, these alterations could cause TDP-43 to mislocalize and become insoluble [16].

In one study, CSF PGRN was measured in three FTLD patients carrying a Ser82fs mutation in the *GRN* gene and this was compared with 24 controls; a threefold reduction of CSF PGRN levels was found in FTLD patients [18]. Two other studies showed also lower PGRN levels in CSF of patients carrying a *GRN* mutation [19, 20]. In these studies no diagnostic value was calculated owing to the small number of patients (n = 5 and n = 3, respectively).

Measuring serum PGRN levels has been shown to be a highly sensitive and specific screening method for identifying *GRN* loss-of-function mutations [21]. Investigating plasma levels of PGRN in patients with *GRN* gene mutations, significant lower levels of PGRN [19, 22] were found. Finch *et al.* reported a diagnostic value of nearly 100% (8 mutation carriers) [22], and Ghidoni *et al.* a specificity of 92.5% and a sensitivity of 100% [19]. However, in FTLD patients without *GRN* mutations, PGRN levels (in CSF and plasma) were comparable to those in control subjects [18–20, 22], and therefore PGRN is not a suitable biomarker for genetically sporadic FTLD.

The papers mentioned above report the specificity of monoclonal antibodies used and the workup/preparation of the enzyme-linked immunosorbent assay (ELISA). However, a complete validation of the ELISA is lacking; usually this includes the determination of a detection limit, recovery, stability, precision, and parallelism [23]. This is something to take into consideration for further studies.

TDP-43 is a 414-amino acid protein that contains two RNA recognition motifs (RRM1 and RRM2) and a glycine-rich C-terminal domain. TDP-43 can act both as a transcriptional repressor and as a splicing regulator. Although physiologic TDP-43 resides mainly in the nucleus, pathology-relevant TDP-43 redistributes from the nucleus to the cytoplasm where it is cleaved and forms phosphorylated and ubiquitinated inclusions [24].

One study found elevated plasma TDP-43 levels in about half of patients clinically diagnosed with FTLN and a quarter of patients with AD [25]. However, there was significant overlap in TDP-43 levels between the two groups. Additionally, some concentrations measured with the ELISA were extremely low, making these measurements less precise [25].

In CSF, there are no well-designed studies measuring TDP-43. An indication of increased CSF TDP-43 levels in FTLN and amyotrophic lateral sclerosis (ALS) was found in one study using a Western blot technique, which is less suitable to quantify TDP-43. Partly overlapping values with the control group were found [26]. Another study also showed increased levels of CSF TDP-43 in ALS patients, especially in the earlier stages [27]. The ELISA probably measured the full-length TDP-43. As a result, sensitivity and usefulness of TDP-43 as a biomarker in clinical practice could be improved by developing ELISA systems that are more specific for pathologic forms of TDP-43, including phosphorylated TDP-43 and its N- or C-terminal fragments. Additionally, CSF TDP-43 measurements in post-mortem-verified FTLN patients would possibly lead to an increased diagnostic accuracy.

CSF tau and P-tau in FTLN patients

FTLD-tau is characterized by pathologic accumulation of intracerebral tau protein, which has been associated with mutations in the tau gene, located on chromosome 17. Intracerebral tau pathology may also be seen in sporadic FTLD cases.

Tau proteins belong to the family of microtubule-associated proteins and are found in axons of neurons. Tau binds microtubules and is essential for growth, stabilization, and transport in neuronal axons.

Six tau isoforms are present in the human brain and they differ by the presence of one or two amino-terminal inserts and by the number of carboxy-terminal repeats (3 or 4 repeats). Different amounts of tau isoforms have been found in CSF of different tauopathies [28–30].

Abnormal phosphorylation of tau is one of the important events in the process leading to aggregation of tau. There are 79 potential serine and threonine phosphorylation sites on the longest tau isoform. Phosphorylation has been reported on approximately 30 of these sites in normal tau proteins. A correlation between the amount of pathologic tau in CSF and the severity of dementia has been demonstrated [31], indicating that this is a reliable marker for neurodegenerative processes. In addition, levels of CSF tau predict the rate of cognitive decline in AD [32–34] and this altered state reflects the elevated levels of P-tau in CSF. The most commonly studied P-tau epitopes are serine181 (P-tau 181) and threonine 231 (P-tau 231) [28, 29, 31].

In FTLD, several pathologic variants have been described in association with abundant intracellular and extracellular hyperphosphorylated filamentous tau inclusions. However, the mere presence of intra-cerebral tau pathology does not necessarily result in increased CSF tau levels. Normal CSF tau levels have been found in FTLD patients with tau mutations [35, 36].

CSF tau levels have been measured in several autopsy-confirmed studies, and the focus was mainly to differentiate FTLD from AD and controls [6, 35, 37–44]. These studies revealed that AD can be distinguished from FTLD and control subjects based on increased CSF tau levels. In FTLD, however, CSF tau levels were comparable to those of controls [6, 35, 37–44]. Looking for the diagnostic value to discriminate FTLD from AD, these studies found a sensitivity and specificity which reaches approximately 80–90%. Different biomarkers and combinations (tau/A β 42 ratio, P-tau/A β 42 ratio, and P-tau) have been used to calculate the sensitivity/specificity.

Within the different pathologic FTLD forms, one study investigated CSF tau in *GRN*-mutated patients, showing levels within normal limits [45]. Bian *et al.* have identified patients with pronounced low levels of CSF tau [35]. These include both FTLD-tau and FTLD-TDP patients; however, a lower trend (not significant) in CSF tau was seen for FTLD-tau patients [36]. Recently, one study showed a lower P-tau/tau ratio in FTLD-TDP compared with FTLD-tau, reaching a sensitivity of 82%. These findings have not yet been replicated [46].

In some of these studies mentioned, two different immunohistochemical platforms to measure CSF tau were merged [35, 36, 38, 44, 47]. The lack of convergence between these two methods needs further study.

Apart from studies in pathologically or genetically proven FTLD, including relatively low patient numbers, the majority of CSF studies in FTLD has been performed in clinically diagnosed cases (see Table 11.1). Although it is believed that clinical diagnosis results in approximately 10–20% underestimation of biomarker accuracy due to misdiagnosis [44], these studies may provide interesting information.

Table 11.1 Schematic overview of CSF studies in FTLD patients (used in this

chapter)

		NFL	P- NFH	TAU	P- TAU	A β 42	A β 40	A β 38	I
1	Arai [82]			C < F					
2	Bian [35]			C, F < A		A < F, C			
3	Bibl [56]			C < F < A		A < F < C			
4	Bibl [69]					F < C	F = A	F < C	
5	Bibl [57]					A < F < C	F < A, C	F < A, C	
6	Bibl [58]			F, C < A	F < C < A	A < F < C	F < C, A	F < C, A	
7	Blasko [13]			F < A	F < A				
8	Borroni [83]			C < F < A	C < F < A				
9	Borroni [84]			C < F < A	C < F < A				
10	Brunnstrom [41]			F < A					
11	Buerger [8]			C, F	C, F				

				$< A$	$< A$				
12	Carecchio [45]			$F =$ C					
13	Clark [37]			$C <$ $F <$ A		$A <$ F, C			
14	de Jong [74]	$C <$ F	$C <$ F	$F <$ A	$F <$ A	$A <$ F			
15	Engelborghs [59]			C, F $< A$	C, F $< A$	$A <$ $F <$ C			
16	Fabre [85]			$C <$ F					
17	Gabelle [60]			$C <$ $F <$ A	C, F $< A$	$A <$ $F <$ C	$F <$ A, C	$F <$ $A <$ C	
18	Ghidoni [19]								I
19	Gloeckner [9]			$C <$ F, A		F, A $< C$	$A <$ F, C		
20	Green [14]			$C <$ $F <$ A					
21	Grossman [38]			C, F $< A$	C, F $< A$	$A <$ F, C			
22	Irwin [47]			$F <$ A					
23	Kapaki [10]			$C <$ $F <$	C, F $< A$	$A <$ $F <$			

			A		C	
24	Kasai [27]					
25	Koopman [40]		F < A	F < A	A < F	
26	Matsuda [86]		F < A			
27	Mecocci [87]		C, F < A			
28	Molina [11]		F < A			
29	Paraskevas [88]		C < F < A			
30	Parnetti [12]		F < A		A < F	
31	Petzold [89]		C < F < A			
32	Philips [20]					I
33	Pijnenburg [64]		C < F < A		A < C, F	
34	Pijnenburg [63]	C = F	C = F	C, F < A	C, F < A	A < C, F
35	Pijnenburg [62]				A < C, F	F < C
36	Riemenschneider		C <		A <	

	[7]		F < A		F < C	
37	Rosso [65]		C < F < A	C, F < A	A < C, F	
38	Schoonenboom [66]		C < F < A	C, F < A	A < C, F	
39	Schoonenboom [6]		C < F < A	C, F < A	A < F < C	
40	Sjögren [61]		C, F < A		A < F < C	
41	Sjögren [73]	C < F	C, F < A			
42	Sjögren [15]		C, F < A	F < C < A		
43	Steinacker [26]					
44	Toledo [44]		C, F < A	C, F < A	A < F < C	
45	Van Damme [18]					I
46	Verwey [67]		C < F < A	F, C < A	A < C, F	F < C
47	Landqvist Waldö [75]	C < A < F	F < A	F < A	A < F	

A = Alzheimer's disease, F = FTLD, C = controls.

In clinically diagnosed FTLD patients, CSF tau values tend to be intermediate between AD and controls and thus most often were slightly increased. Since FTLD usually occurs before the age of 65 years, comparison with AD with early onset (EOAD) is relevant. When only patients with EOAD were compared with FTLD, the difference was even larger, showing much higher levels of tau in AD patients [48].

Considering P-tau levels, several studies found higher levels in FTLD compared with controls, whereas others show similar CSF P-tau levels. When comparing CSF P-tau levels between FTLD patients and AD patients, levels were higher in AD [48].

The diagnostic value of CSF tau and P-tau for identifying FTLD or one of its subgroups seems to be limited, since the differences between groups are small and sometimes inconsistent. Probably, both clinical misdiagnosis and heterogeneity of underlying FTLD pathology contribute to the variation of results. The discrepancy between the findings of a normal to decreased CSF tau in pathologically verified FTLD versus normal to increased CSF tau levels in clinically diagnosed cases, however, warrants further and larger studies in definite FTLD.

CSF amyloid in FTLD patients

Amyloid (A β) is formed after cleavage of the amyloid precursor protein (APP), which is a transmembrane glucoprotein. Proteolytic enzymes, α -, β -, and γ -secretase, cleave APP and A β protein is generated. The γ -secretase, which produces the C-terminal end of the A β peptide, cleaves within the transmembrane region of APP, and can generate a number of isoforms of 36–43 amino acid residues in length. The most common isoforms are A β 40

and A β 42. The A β 40 form is the more common form of the two, but A β 42 is more fibrillogenic [49].

It has been widely demonstrated that CSF tau, P-tau, and A β 42 are reliable biomarkers to identify AD, even in its preclinical stages [50, 51]. The exact relationship between AD neuropathologic change (tau for neurofibrillary pathology and A β 42 for extracellular plaques) and the observed measurement of these peptides in CSF is not known. CSF tau is thought to reflect underlying axonal degeneration. Lower CSF A β 42 in AD may be the result of A β 42 aggregation into extracellular plaques.

In FTLD no cerebral A β 42 amyloidosis is seen and from this perspective, measurement of CSF A β 42 does not seem useful to identify FTLD but may be only helpful in excluding AD neuropathology. Recently, however, several clinical AD cases have been described with AD pathology (confirmed by CSF, or PET, or autopsy), harboring *GRN* mutations [52–55]. A possible link between the *GRN* gene and the type of amyloidosis found in AD is therefore not excluded.

In pathologically confirmed cases, comparable levels of CSF A β 42 were found in FTLD patients and controls (see also Table 11.1). Compared with AD patients, FTLD patients had higher CSF A β 42. In a subset of pathologically confirmed cases, A β 42 seemed to be lower in tau-positive patients than tau-negative patients; however, this was not significant [35, 38].

In clinically defined cohorts, higher levels of CSF A β 42 were found in FTLD compared with AD [6–15]; compared with controls, different results were seen (see Table 11.1). Several publications show lower levels of A β 42 in FTLD [6, 7, 10, 44, 56–61] whereas others show comparable results between FTLD and controls [35, 38, 62–67].

Besides A β 42, also truncated forms of A β have been measured in CSF of FTLD patients, using various methods. CSF A β 38 and A β 40 seem to be

lower in FTLD than controls [56, 62, 67, 68] but when FTLD was compared with AD, discrepant results were found. Several studies showed lower A β 38 and A β 40 in FTLD [57, 62]. Others found comparable results for A β 40 and A β 38 between AD and FTLD [67, 69]. One study applied A β 40 in a model to discriminate FTLD from controls, showing a sensitivity of 87% and specificity of 90% [56]. However, this study used Western blot measurements, and cannot be compared with ELISA studies. Gabelle *et al.* found also lower CSF A β 38 and A β 40 levels in FTLD compared with controls and AD, measured with multiplex kits (Meso-Scale Discovery®) [60]. In this study, when combining P-tau and A β 38, FTLD patients were correctly classified with a sensitivity of 85% and a specificity of 82%.

The suggestion that amyloid biomarkers are probably modified in FTLD raises many questions on the relationship between tau and A β biology. It has been hypothesized that common upstream drivers cause both intracerebral elevation of A β and tau hyperphosphorylation through independent but parallel mechanisms [70]. For example, one of the link hypotheses concerns functioning of the GSK3 (glycogen synthase kinase 3) enzyme. GSK3 phosphorylates the tau peptide to form P-tau which eventually will cluster in filaments. Additionally, GSK3 interacts with presenilin, which in turn is needed for γ -secretase cleavage of A β protein precursor to create A β [71, 72].

In summary, among patients with an FTLD-related clinical syndrome, a normal CSF AD biomarker profile is suggestive of underlying FTLD by ruling out AD pathology. The role of truncated A β forms in the diagnosis of FTLD needs to be further established.

Neurofilaments in FTLD patients

Neurofilament (NF) proteins are major constituents of the neuronal cytoskeleton. Localized in large neurons and myelinated axons, they play an important role in neuronal structure. NFs consist of three polypeptides: the light (NFL, 60 kDa), medium (NFM, 150 kDa), and heavy (NFH, 190–210 kDa) subunits. NFs are likely to be released into the extracellular fluid following neuronal death and axonal degeneration.

Increased levels of NFs in CSF may reflect neuronal degeneration in neurologic disease. Analyses of NFs in CSF of dementia patients have shown conflicting results. CSF NFL levels were increased in FTLD patients compared with controls [73–76]. However, others found comparable results between controls and FTLD patients [63]. These potential CSF biomarkers need further study; to date, to our knowledge, no studies have reported CSF NF measurements in pathologically confirmed FTLD cases.

Non-hypothesis-driven research in FTLD: biomarker discovery

Biomarker discovery uses small and very well-characterized FTLD groups, applying proteomics or other non-immune-based methods.

Recently, in a targeted proteomic search, 151 proteins in CSF of neuropathologic-confirmed FTLD-tau and FTLD-TDP cases have been investigated. In this study no differences were seen in CSF tau and P-tau levels between these two groups. However, other proteins could differentiate these two neuropathologic distinct forms of FTLD; agouti-related peptide, adrenocorticotrophic hormone, Fas, TRAIL-R3 (tumor necrosis factor-related apoptosis-inducing ligand receptor 3), macrophage-derived chemokine, interleukin (IL)-7, IL-23, S100b, and apolipoprotein B.

This strategy seems promising, but these potential biomarkers now need further validation and replication [77].

SELDI-TOF MS (surface-enhanced laser desorption/ionization time-of-flight mass spectrometry) was used to identify novel biomarkers for FTLD [78]. Diagnosis was made clinically in 24 patients and these patients were followed up for at least three years. MRI and SPECT/PET were used to differentiate between rapid or slow FTLD progression. Post-mortem investigation was performed in one patient. Thirteen patients were diagnosed with rapidly progressive FTLD and 11 patients were diagnosed with slowly progressive FTLD. One novel biomarker was detected which differed significantly between rapidly and slowly progressive FTLD. However, till now the identity of this biomarker is not known.

In brain homogenates, one group used quantitative proteomics strategies to identify 194 peptides which were altered in FTLD compared with controls. One of these was septin 11 (SEPT11), which was four times higher in FTLD. Further CSF experiments have to be performed in clinical studies to confirm these findings [79]. Others used post-mortem tissue from FTLD patients for biomarker discovery [80]. Label-free shotgun mass spectrometry (LC-MSE) analysis was used, showing a total of 107 differentially expressed proteins in FTLD compared with controls. One other group performed proteomic analysis with proteins isolated from human cortex of FTLD patients [81]. By 2D gel electrophoresis and MALDI-TOF (matrix-assisted laser desorption/ionization – time of flight) a total of 24 proteins were identified which were differentially expressed in this group of patients. Again, all these promising results have to be confirmed in CSF in clinical patients.

The non-hypothetical investigations mentioned here are trying to classify subtypes of FTLD based on brain molecular profiles. Further studies in this area will hopefully clarify the molecular changes in FTLD

brains and will drive studies towards the development of biomarkers that can be used for better classification of these subjects.

Summary

In patients with clinically diagnosed FTLN, AD biomarkers can be helpful to exclude AD as a possible cause. Co-morbidity of AD and FTLN, however, cannot be excluded using this approach, especially in elderly patients.

This step would ideally be followed by the measurement of new biomarkers which can distinguish between the different types of FTLN. Based on proteomics studies some progress is being made towards this step.

There are several biomarkers that warrant further investigation in neuropathologically confirmed cases. Among these are the truncated forms of A β as well as different isoforms of tau. Additionally, TDP-43, PGRN, GRN fragments, and NFs are promising biomarkers, which need to be further investigated with robust measurement systems.

The first results of proteomic studies yielded a high number of candidate proteins relevant for the pathophysiology of FTLN. A major concern is that the findings of these studies need to be replicated and that protein markers have to be validated using ELISAs.

It remains a scientific endeavor to develop a set of CSF biomarkers that reliably identifies the main FTLN neuropathologic subgroups to eventually effectively implement disease-modifying therapies.

References

1. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;**51**(6):1546–54.

2. Mackenzie IR, Foti D, Woulfe J, Hurwitz TA. Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions. *Brain* 2008;**131**(Pt 5):1282–93.

3. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001;**58**(11):1803–9.

4. Mackenzie IR, Munoz DG, Kusaka H, Yokota O, Ishihara K, Roeber S, *et al.* Distinct pathological subtypes of FTLTD-FUS. *Acta Neuropathol* 2011;**121**(2):207–18.

5. Consensus report of the Working Group on: “Molecular and Biochemical Markers of Alzheimer's Disease.” The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group. *Neurobiol Aging* 1998;**19**(2):109–16.

6. Schoonenboom NS, Reesink FE, Verwey NA, Kester MI, Teunissen CE, van de Ven PM, *et al.* Cerebrospinal fluid markers for differential dementia diagnosis in a large memory clinic cohort. *Neurology* 2012;**78**(1):47–54.

7. Riemenschneider M, Wagenpfeil S, Diehl J, Lautenschlager N, Theml T, Heldmann B, *et al.* Tau and Abeta42 protein in CSF of patients with frontotemporal degeneration. *Neurology* 2002;**58**(11):1622–8.

8. Buerger K, Zinkowski R, Teipel SJ, Tapiola T, Arai H, Blennow K, *et al.* Differential diagnosis of Alzheimer disease with cerebrospinal fluid levels of tau protein phosphorylated at threonine 231. *Arch Neurol* 2002;**59**(8):1267–72.

-
9. Gloeckner SF, Meyne F, Wagner F, Heinemann U, Krasnianski A, Meissner B, *et al.* Quantitative analysis of transthyretin, tau and amyloid-beta in patients with dementia. *J Alzheimers Dis* 2008;**14**(1):17–25.
-
10. Kapaki E, Paraskevas GP, Papageorgiou SG, Bonakis A, Kalfakis N, Zalonis I, *et al.* Diagnostic value of CSF biomarker profile in frontotemporal lobar degeneration. *Alzheimer Dis Assoc Disord* 2008;**22**(1):47–53.
-
11. Molina L, Touchon J, Herpe M, Lefranc D, Duplan L, Cristol JP, *et al.* Tau and apo E in CSF: potential aid for discriminating Alzheimer's disease from other dementias. *Neuroreport* 1999;**10**(17):3491–5.
-
12. Parnetti L, Lanari A, Saggese E, Spaccatini C, Gallai V. Cerebrospinal fluid biochemical markers in early detection and in differential diagnosis of dementia disorders in routine clinical practice. *Neurol Sci* 2003;**24**(3):199–200.
-
13. Blasko I, Lederer W, Oberbauer H, Walch T, Kemmler G, Hinterhuber H, *et al.* Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. *Dement Geriatr Cogn Disord* 2006;**21**(1):9–15.
-
14. Green AJ, Harvey RJ, Thompson EJ, Rossor MN. Increased tau in the cerebrospinal fluid of patients with frontotemporal dementia and Alzheimer's disease. *Neurosci Lett* 1999;**259**(2):133–5.
-
15. Sjögren M, Davidsson P, Tullberg M, Minthon L, Wallin A, Wikkelso C, *et al.* Both total and phosphorylated tau are increased in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001;**70**(5):624–30.
-
16. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol* 2012;**8**(8):423–34.
-
17. Ghidoni R, Paterlini A, Benussi L. Circulating progranulin as a biomarker for neurodegenerative diseases. *Am J Neurodegener Dis* 2012;**1**(2):180–90.
-

-
- 18.** Van Damme P, Van Hoecke A, Lambrechts D, Vanacker P, Bogaert E, van Switten J, *et al.* Progranulin functions as a neurotrophic factor to regulate neurite outgrowth and enhance neuronal survival. *J Cell Biol* 2008;**181**(1):37–41.
-
- 19.** Ghidoni R, Benussi L, Glionna M, Franzoni M, Binetti G. Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration. *Neurology* 2008;**71**(16):1235–9.
-
- 20.** Philips T, De Muynck L, Thu HN, Weynants B, Vanacker P, Dhondt J, *et al.* Microglial upregulation of progranulin as a marker of motor neuron degeneration. *J Neuropathol Exp Neurol* 2010;**69**(12):1191–200.
-
- 21.** Sleegers K, Brouwers N, Van Damme P, Engelborghs S, Gijselinck I, van der Zee J, *et al.* Serum biomarker for progranulin-associated frontotemporal lobar degeneration. *Ann Neurol* 2009;**65**(5):603–9.
-
- 22.** Finch N, Baker M, Crook R, Swanson K, Kuntz K, Surtees R, *et al.* Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. *Brain* 2009;**132**(Pt 3):583–91.
-
- 23.** Wild D. *The Immunoassay Handbook*, 2nd edn. New York, NY: Nature Publishing Group; 2001.
-
- 24.** Mackenzie IR, Rademakers R. The molecular genetics and neuropathology of frontotemporal lobar degeneration: recent developments. *Neurogenetics* 2007;**8**(4):237–48.
-
- 25.** Foulds P, McAuley E, Gibbons L, Davidson Y, Pickering-Brown SM, Neary D, *et al.* TDP-43 protein in plasma may index TDP-43 brain pathology in Alzheimer's disease and frontotemporal lobar degeneration. *Acta Neuropathol* 2008;**116**(2):141–6.
-
- 26.** Steinacker P, Hendrich C, Sperfeld AD, Jesse S, von Arnim CA, Lehnert S, *et al.* TDP-43 in cerebrospinal fluid of patients with frontotemporal lobar

degeneration and amyotrophic lateral sclerosis. *Arch Neurol* 2008;**65**(11):1481–7.

27. Kasai T, Tokuda T, Ishigami N, Sasayama H, Foulds P, Mitchell DJ, *et al.* Increased TDP-43 protein in cerebrospinal fluid of patients with amyotrophic lateral sclerosis. *Acta Neuropathol* 2009;**117**(1):55–62.

28. Sergeant N, Delacourte A, Buee L. Tau protein as a differential biomarker of tauopathies. *Biochim Biophys Acta* 2005;**1739**(2–3):179–97.

29. Sergeant N, Bretteville A, Hamdane M, Caillet-Boudin ML, Grognet P, Bombois S, *et al.* Biochemistry of tau in Alzheimer's disease and related neurological disorders. *Expert Rev Proteomics* 2008;**5**(2):207–24.

30. Luk C, Compta Y, Magdalinou N, Marti MJ, Hondhamuni G, Zetterberg H, *et al.* Development and assessment of sensitive immuno-PCR assays for the quantification of cerebrospinal fluid three- and four-repeat tau isoforms in tauopathies. *J Neurochem* 2012;**123**(3):396–405.

31. Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Brain Res Rev* 2000;**33**(1):95–130.

32. Kester MI, van der Vlies AE, Blankenstein MA, Pijnenburg YA, Van Elk EJ, Scheltens P, *et al.* CSF biomarkers predict rate of cognitive decline in Alzheimer disease. *Neurology* 2009;**73**(17):1353–8.

33. van Rossum IA, Vos SJ, Burns L, Knol DL, Scheltens P, Soininen H, *et al.* Injury markers predict time to dementia in subjects with MCI and amyloid pathology. *Neurology* 2012;**79**(17):1809–16.

34. van Rossum IA, Visser PJ, Knol DL, van der Flier WM, Teunissen CE, Barkhof F, *et al.* Injury markers but not amyloid markers are associated with rapid progression from mild cognitive impairment to dementia in Alzheimer's disease. *J Alzheimers Dis* 2012;**29**(2):319–27.

-
- 35.** Bian H, van Swieten JC, Leight S, Massimo L, Wood E, Forman M, *et al.* CSF biomarkers in frontotemporal lobar degeneration with known pathology. *Neurology* 2008;**70**(19 Pt 2):1827–35.
-
- 36.** Hu WT, Trojanowski JQ, Shaw LM. Biomarkers in frontotemporal lobar degenerations – progress and challenges. *Prog Neurobiol* 2011;**95**(4):636–48.
-
- 37.** Clark CM, Xie S, Chittams J, Ewbank D, Peskind E, Galasko D, *et al.* Cerebrospinal fluid tau and beta-amyloid: how well do these biomarkers reflect autopsy-confirmed dementia diagnoses? *Arch Neurol* 2003;**60**(12):1696–702.
-
- 38.** Grossman M, Farmer J, Leight S, Work M, Moore P, Van Deerlin, V, *et al.* Cerebrospinal fluid profile in frontotemporal dementia and Alzheimer's disease. *Ann Neurol* 2005;**57**(5):721–9.
-
- 39.** Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, *et al.* Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain* 2013;**136**(Pt 9):2697–706.
-
- 40.** Koopman K, Le Bastard N, Martin JJ, Nagels G, De Deyn PP, Engelborghs S. Improved discrimination of autopsy-confirmed Alzheimer's disease (AD) from non-AD dementias using CSF P-tau (181P). *Neurochem Int* 2009;**55**(4):214–18.
-
- 41.** Brunnstrom H, Rawshani N, Zetterberg H, Blennow K, Minthon L, Passant U, *et al.* Cerebrospinal fluid biomarker results in relation to neuropathological dementia diagnoses. *Alzheimers Dement* 2010;**6**(2):104–9.
-
- 42.** Engelborghs S, De Vreese K, Van de Castele T, Vanderstichele H, Van Everbroeck B, Cras P, *et al.* Diagnostic performance of a CSF-biomarker panel in autopsy-confirmed dementia. *Neurobiol Aging* 2008;**29**(8):1143–59.
-
- 43.** Tapiola T, Alafuzoff I, Herukka SK, Parkkinen L, Hartikainen P, Soininen H,

et al. Cerebrospinal fluid β -amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch Neurol* 2009;**66**(3):382–9.

44. Toledo JB, Brettschneider J, Grossman M, Arnold SE, Hu WT, Xie SX, *et al.* CSF biomarkers cutoffs: the importance of coincident neuropathological diseases. *Acta Neuropathol* 2012;**124**(1):23–35.

45. Carecchio M, Fenoglio C, Cortini F, Comi C, Benussi L, Ghidoni R, *et al.* Cerebrospinal fluid biomarkers in progranulin mutations carriers. *J Alzheimers Dis* 2011;**27**(4):781–90.

46. Hu WT, Watts K, Grossman M, Glass J, Lah JJ, Hales C, *et al.* Reduced CSF p-Tau181 to Tau ratio is a biomarker for FTLD-TDP. *Neurology* 2013;**81**(22):1945–52.

47. Irwin DJ, McMillan CT, Toledo JB, Arnold SE, Shaw LM, Wang LS, *et al.* Comparison of cerebrospinal fluid levels of tau and Abeta 1–42 in Alzheimer disease and frontotemporal degeneration using 2 analytical platforms. *Arch Neurol* 2012;**69**(8):1018–25.

48. van Harten AC, Kester MI, Visser PJ, Blankenstein MA, Pijnenburg YA, van der Flier WM, *et al.* Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. *Clin Chem Lab Med* 2011;**49**(3):353–66.

49. Hartmann T, Bieger SC, Bruhl B, Tienari PJ, Ida N, Allsop D, *et al.* Distinct sites of intracellular production for Alzheimer's disease Abeta40/42 amyloid peptides. *Nat Med* 1997;**3**(9):1016–20.

50. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. *Lancet Neurol* 2003;**2**(10):605–13.

51. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, *et al.* CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA* 2009;**302**(4):385–93.

52. Perry DC, Lehmann M, Yokoyama JS, Karydas A, Lee JJ, Coppola G, *et al.* Progranulin mutations as risk factors for Alzheimer disease. *JAMA Neurol* 2013;**70**(6):774–8.

53. Rademakers R, Baker M, Gass J, Adamson J, Huey ED, Momeni P, *et al.* Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C→T (Arg493X) mutation: an international initiative. *Lancet Neurol* 2007;**6**(10):857–68.

54. Josephs KA, Ahmed Z, Katsuse O, Parisi JF, Boeve BF, Knopman DS, *et al.* Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclusions with progranulin gene (*PGRN*) mutations. *J Neuropathol Exp Neurol* 2007;**66**(2):142–51.

55. Brouwers N, Sleegers K, Engelborghs S, Maurer-Stroh S, Gijselinck I, van der Zee J, *et al.* Genetic variability in progranulin contributes to risk for clinically diagnosed Alzheimer disease. *Neurology* 2008;**71**(9):656–64.

56. Bibl M, Mollenhauer B, Wolf S, Esselmann H, Lewczuk P, Kornhuber J, *et al.* Reduced CSF carboxyterminally truncated Abeta peptides in frontotemporal lobe degenerations. *J Neural Transm* 2007;**114**(5):621–8.

57. Bibl M, Gallus M, Welge V, Esselmann H, Wolf S, Ruther E, *et al.* Cerebrospinal fluid amyloid-beta 2–42 is decreased in Alzheimer's, but not in frontotemporal dementia. *J Neural Transm* 2012;**119**(7):805–13.

58. Bibl M, Mollenhauer B, Lewczuk P, Esselmann H, Wolf S, Otto M, *et al.* Cerebrospinal fluid tau, p-tau 181 and amyloid-beta38/40/42 in frontotemporal dementias and primary progressive aphasia. *Dement Geriatr Cogn Disord* 2011;**31**(1):37–44.

59. Engelborghs S, Maertens K, Vloeberghs E, Aerts T, Somers N, Marien P, *et al.* Neuropsychological and behavioural correlates of CSF biomarkers in dementia. *Neurochem Int* 2006;**48**(4):286–95.

60. Gabelle A, Roche S, Geny C, Bennys K, Labauge P, Tholance Y, *et al.* Decreased sA β PP β , A β 38, and A β 40 cerebrospinal fluid levels in frontotemporal dementia. *J Alzheimers Dis* 2011;**26**(3):553–63.

61. Sjögren M, Minthon L, Davidsson P, Granerus A-K, Clarberg A, Vanderstichele H, *et al.* CSF levels of tau, beta-amyloid(1–42) and GAP-43 in frontotemporal dementia, other types of dementia and normal aging. *J Neural Transm* 2000;**107**(5):563–79.

62. Pijnenburg YA, Schoonenboom SN, Mehta PD, Mehta SP, Mulder C, Veerhuis R, *et al.* Decreased cerebrospinal fluid amyloid beta (1–40) levels in frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry* 2007;**78**(7):735–7.

63. Pijnenburg YA, Janssen JC, Schoonenboom NS, Petzold A, Mulder C, Stigbrand T, *et al.* CSF neurofilaments in frontotemporal dementia compared with early onset Alzheimer's disease and controls. *Dement Geriatr Cogn Disord* 2007;**23**(4):225–30.

64. Pijnenburg YA, Schoonenboom NS, Rosso SM, Mulder C, Van Kamp GJ, van Swieten JC, *et al.* CSF tau and A β 42 are not useful in the diagnosis of frontotemporal lobar degeneration. *Neurology* 2004;**62**(9):1649.

65. Rosso SM, van Herpen E, Pijnenburg YA, Schoonenboom NS, Scheltens P, Heutink P, *et al.* Total tau and phosphorylated tau 181 levels in the cerebrospinal fluid of patients with frontotemporal dementia due to P301L and G272V tau mutations. *Arch Neurol* 2003;**60**(9):1209–13.

66. Schoonenboom NS, Pijnenburg YA, Mulder C, Rosso SM, Van Elk EJ, Van Kamp GJ, *et al.* Amyloid beta(1–42) and phosphorylated tau in CSF as markers for early-onset Alzheimer disease. *Neurology* 2004;**62**(9):1580–4.

67. Verwey NA, Kester MI, van der Flier WM, Veerhuis R, Berkhof H, Twaalfhoven H, *et al.* Additional value of CSF amyloid-beta 40 levels in the

differentiation between FTLT and control subjects. *J Alzheimers Dis* 2010;**20**(2):445–52.

68. Gabelle A, Roche S, Geny C, Bennys K, Labauge P, Tholance Y, *et al.* Correlations between soluble alpha/beta forms of amyloid precursor protein and Abeta38, 40, and 42 in human cerebrospinal fluid. *Brain Res* 2010;**1357**:175–83.

69. Bibl M, Lewczuk P, Esselmann H, Mollenhauer B, Klafki HW, Welge V, *et al.* CSF amyloid-beta 1–38 and 1–42 in FTD and AD: biomarker performance critically depends on the detergent accessible fraction. *Proteomics Clin Appl* 2008;**2**(10–11):1548–56.

70. Small SA, Duff K. Linking Abeta and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. *Neuron* 2008;**60**(4):534–42.

71. Phiel CJ, Wilson CA, Lee VM, Klein PS. GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides. *Nature* 2003;**423**(6938):435–9.

72. Schaffer BA, Bertram L, Miller BL, Mullin K, Weintraub S, Johnson N, *et al.* Association of GSK3B with Alzheimer disease and frontotemporal dementia. *Arch Neurol* 2008;**65**(10):1368–74.

73. Sjögren M, Rosengren L, Minthon L, Davidsson P, Blennow K, Wallin A. Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. *Neurology* 2000;**54**(10):1960–4.

74. de Jong D, Jansen RW, Pijnenburg YA, van Geel WJ, Borm GF, Kremer HP, *et al.* CSF neurofilament proteins in the differential diagnosis of dementia. *J Neurol Neurosurg Psychiatry* 2007;**78**(9):936–8.

75. Landqvist Waldö M, Frizell SA, Passant U, Zetterberg H, Rosengren L, Nilsson C, *et al.* Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia. *BMC Neurol* 2013;**13**:54.

76. Petzold A, Keir G, Warren J, Fox N, Rossor MN. A systematic review and

meta-analysis of CSF neurofilament protein levels as biomarkers in dementia. *Neurodegener Dis* 2007;**4**(2–3):185–94.

77. Hu WT, Chen-Plotkin A, Grossman M, Arnold SE, Clark CM, Shaw LM, *et al.* Novel CSF biomarkers for frontotemporal lobar degenerations. *Neurology* 2010;**75**(23):2079–86.

78. Mattsson N, Ruetschi U, Pijnenburg YA, Blankenstein MA, Podust VN, Li S, *et al.* Novel cerebrospinal fluid biomarkers of axonal degeneration in frontotemporal dementia. *Mol Med Rep* 2008 Sep;**1**(5):757–61.

79. Gozal YM, Seyfried NT, Gearing M, Glass JD, Heilman CJ, Wu J, *et al.* Aberrant septin 11 is associated with sporadic frontotemporal lobar degeneration. *Mol Neurodegener* 2011;**6**:82.

80. Martins-de-Souza D, Guest PC, Mann DM, Roeber S, Rahmoune H, Bauder C, *et al.* Proteomic analysis identifies dysfunction in cellular transport, energy, and protein metabolism in different brain regions of atypical frontotemporal lobar degeneration. *J Proteome Res* 2012;**11**(4):2533–43.

81. Schweitzer K, Decker E, Zhu L, Miller RE, Mirra SS, Spina S, *et al.* Aberrantly regulated proteins in frontotemporal dementia. *Biochem Biophys Res Commun* 2006;**348**(2):465–72.

82. Arai H, Morikawa Y, Higuchi M, Matsui T, Clark CM, Miura M, *et al.* Cerebrospinal fluid tau levels in neurodegenerative diseases with distinct tau-related pathology. *Biochem Biophys Res Commun* 1997;**236**(2):262–4.

83. Borroni B, Gardoni F, Parnetti L, Magno L, Malinverno M, Saggese E, *et al.* Pattern of tau forms in CSF is altered in progressive supranuclear palsy. *Neurobiol Aging* 2009;**30**(1):34–40.

84. Borroni B, Malinverno M, Gardoni F, Alberici A, Parnetti L, Premi E, *et al.* Tau forms in CSF as a reliable biomarker for progressive supranuclear palsy. *Neurology* 2008;**71**(22):1796–803.

-
- 85.** Fabre SF, Forsell C, Viitanen M, Sjögren M, Wallin A, Blennow K, *et al.* Clinic-based cases with frontotemporal dementia show increased cerebrospinal fluid tau and high apolipoprotein E epsilon4 frequency, but no tau gene mutations. *Exp Neurol* 2001;**168**(2):413–18.
-
- 86.** Matsuda K, Tashiro K, Hayashi Y, Monji A, Yoshida I, Mitsuyama Y. Measurement of laminins in the cerebrospinal fluid obtained from patients with Alzheimer's disease and vascular dementia using a modified enzyme-linked immunosorbent assay. *Dement Geriatr Cogn Disord* 2002;**14**(3):113–22.
-
- 87.** Mecocci P, Cherubini A, Bregnocchi M, Chionne F, Cecchetti R, Lowenthal DT, *et al.* Tau protein in cerebrospinal fluid: a new diagnostic and prognostic marker in Alzheimer disease? *Alzheimer Dis Assoc Disord* 1998;**12**(3):211–14.
-
- 88.** Paraskevas GP, Kapaki E, Liappas I, Theotoka I, Mamali I, Zournas C, *et al.* The diagnostic value of cerebrospinal fluid tau protein in dementing and nondementing neuropsychiatric disorders. *J Geriatr Psychiatry Neurol* 2005;**18**(3):163–73.
-
- 89.** Petzold A, Chapman MD, Schraen S, Verwey NA, Pasquier F, Bombois S, *et al.* An unbiased, staged, multicentre, validation strategy for Alzheimer's disease CSF tau levels. *Exp Neurol* 2010;**223**(2):432–8.

Chapter 12

Genetic counseling for FTD



Jill S. Goldman and Elisabeth McCarty Wood

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

Mr. A. is a 56-year-old man with a two-year history of behavioral and personality change. Mr. and Mrs. A. are referred for genetic counseling by the neurologist because Mr. A. has received a diagnosis of frontotemporal dementia (FTD) and has a family history of neurologic disease. Although Mr. A. appears unconcerned, Mrs. A. seems anxious and immediately says, “I don't know why we're here as nobody in the family has anything like this!” The genetic counselor acknowledges that thinking about a heredity condition is scary, but that it is important for family information as well as to determine the cause of Mr. A.'s disease.

A review of family history reveals that Mr. A. is the second oldest in a sibship of four. Mr. A.'s father died of an acute

myocardial infarction at age 50. His mother is still living independently. Mr. A. reports that his siblings are fine. But when questioned about psychiatric disease, Mrs. A. reports that Mr. A.'s older brother has been alienated from the family because he is a “drug addict and crazy,” and they know little about him. The other person who suffers from a psychiatric problem is one of Mr. A.'s paternal cousins. He is so depressed that he didn't even attend the recent family reunion. Apparently this 58-year-old man had been fine after his mother died from Parkinson's disease (PD) at the age of 68, but now that he is nearing her age of onset, the family believes he has “post-traumatic stress disorder.” His mother developed dementia as well as parkinsonism, and was very hard to manage. This cousin seems to have lost interest in everything, even his daughter who is to be married. Three of Mr. A.'s grandparents lived into their 80s and died of strokes and cancer. His paternal grandmother died at about age 70 in a nursing home, but the cause of her death was never discussed. No one else in the family has neurologic or psychiatric problems. Mr. and Mrs. A. have three children ages 23, 20, and 18.

The genetic counselor reviews the symptoms and genetics of FTD, emphasizing the variability of symptoms that can occur, even within a family. She uses Mr. A.'s family pedigree to explain why the neurologist referred them for genetic counseling, pointing to the possibility that Mr. A.'s brother and cousin, as well as his aunt, might also have symptoms of FTD. His father may have died too young to show symptoms, and his grandmother may have had the disease as well. Mr. A. remains indifferent, but Mrs. A. starts to cry. She admits to being terrified of learning that Mr. A. carries hereditary FTD. She doesn't want to have to tell her children,

especially her older daughter who is engaged. Again the counselor acknowledges her fear but repeats that the information could provide the family with information for life planning, especially reproductive planning. She suggested that they go home and have a family meeting with their children, and perhaps Mr. A.'s two sisters, to discuss whether or not they want to pursue genetic testing.

Learning that a loved one has FTD is extremely difficult, but learning that the disease could have a genetic origin is terrifying. Some families have watched previous generations suffer from the disease. For them, seeing someone of their own generation with symptoms both revives past nightmares and confirms the fear that this might happen to them. For families in which a possible hereditary FTD diagnosis is new (because of lost family history, early death of relatives, or wrong diagnoses), the prospect of genetic testing can be overwhelming. Genetic counseling for these families can provide accurate information, assistance navigating the process of deciding whether or not to proceed with genetic testing, and support both before and after testing. FTD's many unique and complicated factors make genetic counseling particularly challenging. It is a heterogeneous disease from start to finish – different etiologies (sporadic and genetic), genetic heterogeneity, variable symptomology, and pathologic heterogeneity. Thus, wrong or delayed diagnoses, familial disease experience, inability to predict age of onset or disease course, and often family dysfunction contribute to highly emotional and complex genetic counseling sessions. Through a series of case histories, this chapter will describe the process of genetic counseling for hereditary FTD.

The introductory case history presents several important aspects of the genetic counseling process. In recognizing the variable symptoms of FTD,

the neurologist took a three-generation family history, which included not only dementia, but also other neurologic and psychiatric conditions. Although Mr. A.'s cousin's and brother's psychiatric problems could have been unrelated to any neurologic condition and his aunt could have had PD dementia, Lewy body disease, or PD with Alzheimer's disease (AD), these conditions also overlap with the FTD phenotype. The neurologist perceptively opted to raise the possibility of a genetic etiology and offer genetic counseling to explore it further. Appropriate referrals for genetic counseling include symptomatic or asymptomatic people with possible family histories of a genetic disorder, or even individuals questioning whether a disorder is genetic. Importantly, a genetic counseling referral does not necessitate genetic testing, but is instead, a time for exploration, education, and guidance. Making the distinction between counseling and testing can be essential for those patients who are hesitant to proceed with testing. Since genetic testing is elective, all patients should receive pre-test as well as post-test counseling so that they can make an informed decision about testing and be prepared to handle genetic test results.

Case 1

Mr. G. presents in neurology clinic with complaints of word-finding difficulty. He is a 56-year-old White male with 16 years of education. He was a high school history teacher until last year, when he took early retirement because he was having difficulty performing his teaching duties. During his evaluation, he shares that he always felt destined to develop AD because both his mother and her brother had it. He has researched the genetics of AD on the Internet and requests that the doctor provide him with genetic testing for AD. He regrets not knowing more about the cause of his mother's

disease, and wants to have any diagnostic information available to share with his two children, ages 28 and 25. After discussing a probable diagnosis of primary progressive aphasia, the neurologist explains that this diagnosis can be due to underlying AD, frontotemporal lobar degeneration (FTLD), or other pathologies. Based on Mr. G.'s request, he provides an order for *PSEN1* genetic testing, and also a referral for genetic counseling, encouraging the consultation as part of a thorough investigation of family history concerns.

Mr. G. and his wife attend the genetic counseling session together. Mr. G. comments that he had been concerned about a genetic form of AD, but recently learned that his *PSEN1* genetic test was negative; he is relieved by the result. The genetic counselor acknowledges that having a family history of a condition like AD can be concerning and asks Mr. G. to share more about his experiences with the disease in his family. Mr. G. explains that his mother became depressed in her mid-50s, which was attributed to her husband's death. She became more withdrawn and gradually stopped speaking. She was mute by age 62. She fell several times and was wheelchair bound by age 64. She died at 65 after a brief illness; there was no autopsy. Mr. G. becomes emotional while discussing his mother, saying that despite the negative *PSEN1* result, he still fears this will be his same fate. Mrs. G. tells the genetic counselor that his mother had a sister and a brother. Her sister is alive and well at age 80, but her brother had a rapidly progressive dementia. The genetic counselor asks about the uncle's disease progression. They believe his onset was around age 50. He was first suspected of having a psychiatric disease because of changes in his personality and behaviors, but was then diagnosed with early-onset

AD. His cousins struggled to find appropriate care for him, given his young age and good physical health; he was eventually placed in the dementia unit of a nursing home. He died at 55. An autopsy was not performed. Mr. G. has limited information about his maternal grandparents, but says there are family stories that his grandfather became senile in later years. His paternal family history is unremarkable. There is no known family history of amyotrophic lateral sclerosis (ALS) or PD.

The genetic counselor reviews the genetics of early-onset AD and Mr. G.'s previous testing for *PSEN1*. She then explains that while AD is the most common form of dementia, other forms of neurodegenerative disease, such as FTD, can also be hereditary; additionally, other genes besides *PSEN1* can cause AD. They discuss the difficulty, especially in previous generations, of making dementia diagnoses. The genetic counselor explains that it will be impossible to know his mother's and uncle's exact disease, but given their symptoms, FTD is certainly a possibility. She reviews the currently known genetic causes of FTD, with an emphasis on the three most common genes, *MAPT*, *GRN*, and *C9orf72*. The genetic counselor asks Mr. and Mrs. G. if they have discussed the family history concerns and genetic testing with their two adult children. The couple notes they would prefer to initiate this conversation if a genetic cause is found, as they do not want to worry their children when no further action can be taken. The genetic counselor reviews clinical genetic testing options for the known FTD genes. In discussing a plan for genetic testing, the genetic counselor explains that they can use Mr. G.'s symptoms and family history to first test the most likely gene, using guidance from published literature, or order a panel of all known FTD genes. Mr. G. states that he would

be most comfortable testing all the known FTD genes, to avoid false reassurance from a single negative test, as he had with *PSEN1*. The genetic counselor reviews a plan for clinical genetic testing and coordinates this testing plan with Mr. G.'s neurologist.

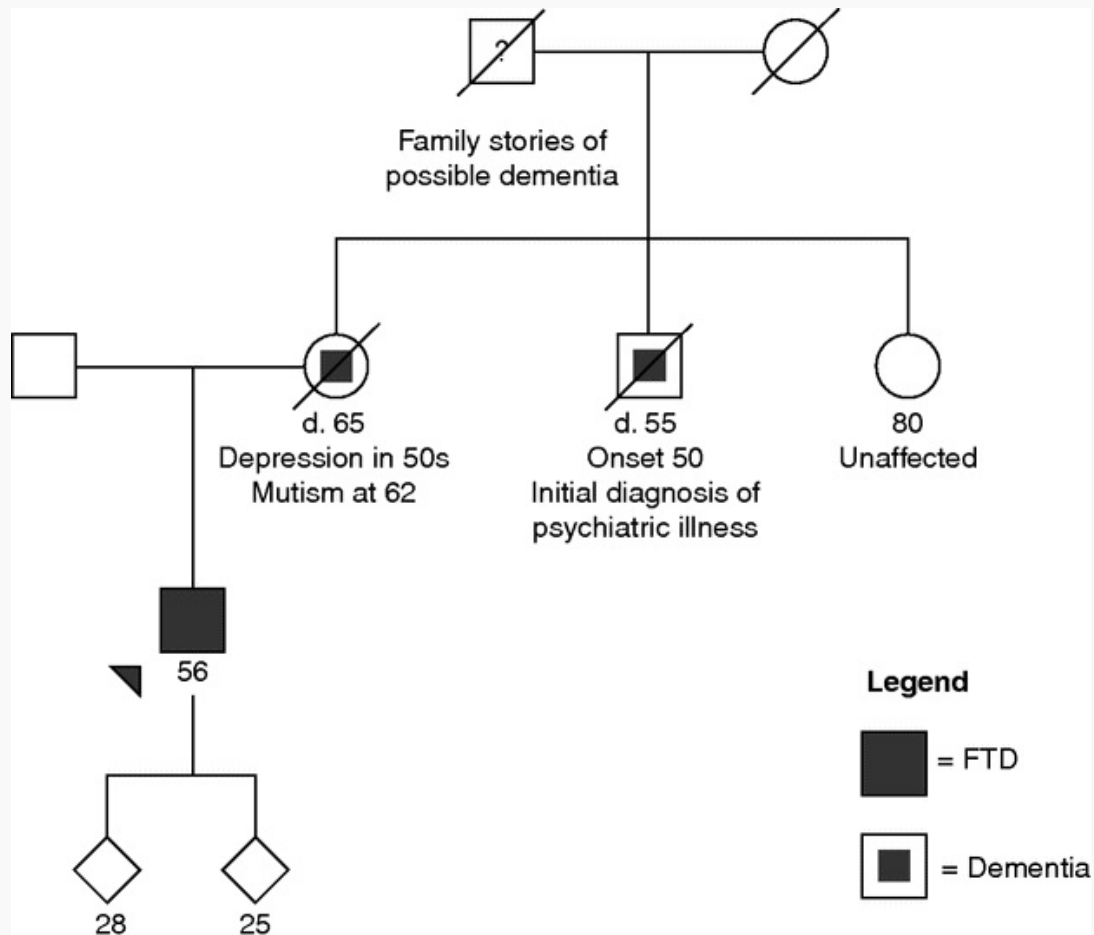


Figure 12.1 Pedigree for Case 1.

The genetic counselor and neurologist meet with Mr. and Mrs. G. for the disclosure of the genetic testing results, which are positive for a known mutation in progranulin (*GRN*). Mr. G. is not surprised by this news, but is emotional over the confirmed risk to his children. The genetic counselor answers Mr. and Mrs. G.'s initial questions about the genetic test result. This leads into a discussion with the neurologist of its impact on his clinical diagnosis. A review of Mr. G.'s clinical evaluation is consistent

with FTD. The genetic counselor contracts with them to follow up by phone, and to have an in-person meeting in one month.

By professional definition, genetic counselors help people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. Genetic counseling is often a process, not a single session, involving interpretation of family and medical histories, education about inheritance, testing, management, prevention, resources, and research, and counseling to promote informed choices and adaptation to the risk or condition [1]. Given how rapidly genetics has entered the medical landscape, it is not surprising that genetic counselors are increasingly in demand for many specialty clinics.

Like many health professionals, genetic counselors can serve different roles, depending on the particular needs of a case. In the case of Mr. G., the genetic counselor's initial role focuses on the collection and interpretation of the family history. Eliciting detailed family history information is a cornerstone of the genetic counseling process. In many cases, the dialogue surrounding the family history is the first interaction between the genetic counselor and patient, not only setting the stage for the next steps but also establishing a connection between the two parties. A detailed family history is an important diagnostic tool and one of the key issues in providing genetic counseling in the FTD setting [2, 3]. The collection of family history should not only focus on classic dementia symptoms, but also psychiatric histories and symptoms of movement disorders such as parkinsonism and motor neuron disease. A particular challenge in the collection of an FTD-specific pedigree is that many diagnostic terms currently used may not have been used in previous generations. Therefore, care is taken to note as many details as known about the age of onset and clinical symptoms from initial

onset onward, or even to elicit family stories concerning a relative with possible neurodegenerative disease. Due to the behavioral and personality changes associated with FTD, family histories of psychiatric symptoms are not uncommon. Family histories that include the onset of psychiatric diagnoses later in adulthood should be considered with the same attention given to more classic reports of neurodegenerative disease. The resulting detailed pedigree, typically encompassing three or more generations, holds vital information that can be used to guide genetic testing decisions for the patient and family.

Quick tips to eliciting pedigrees in the FTD setting

The following points can help detect reduced penetrance, which can hide or minimize a classic autosomal dominant pattern of inheritance:

- Collect first- and second-degree relatives (children, siblings, parents, aunts/uncles, and grandparents)
- Document current ages and ages at death
- Do not assume a relative with late-onset neurodegenerative disease does not contribute to a possible genetic pattern

Misdiagnosis of FTD is common, especially in previous generations. The following points directly address common misdiagnosis concerns:

- For relatives with neurodegenerative disease, document as many clinical details as possible, such as age and symptoms at onset, symptom progression, and source of diagnosis (e.g., family report, primary care physician, specialist, autopsy)

- For relatives with movement disorders, ask about co-occurrence of cognitive decline (e.g., Parkinson's disease with dementia) and vice versa (e.g., Alzheimer's disease with parkinsonism)
- Ask specifically if any relatives had diagnoses of mental illness, nervous breakdowns, or other psychiatric concerns during adulthood. Document details such as ages of onset, symptoms, successful or unsuccessful treatments, or even just family stories about the individual's symptoms and behavior
- For histories of substance abuse, document any details known about other difficulties, either physical or psychiatric, as well as any successful treatment or recovery periods

The discussion of genetic contribution to disease can bring a complicated combination of science and emotions. While genetics is often referenced in the news and popular literature, many patients do not have a high level of genetics education. Trying to absorb new genetic information, as well as information about FTD itself, can be overwhelming. Genetic counseling provides genetics education in more patient-friendly terms. Genetic counseling can also address the preconceived beliefs learned from friends or family members or through self-education most often via the Internet. However, with the understanding of genetics and inheritance, emotional responses such as sadness, fear, and guilt can arise. Genetic counseling should support and guide patients, as well as the patient's family since genetic information rarely impacts the patient in isolation. As illustrated in many of the case examples, a genetic diagnosis in a patient will often lead to additional family members contacting the genetic counselor with questions and concerns of their own. In some cases, the

genetic counselor may be able to take on these additional individuals as patients in their own right, providing them with the same level of personalized attention and care as their family member has received. Genetic counselors often serve as guides to the patient and family in their search of additional resources (e.g., support groups, psychiatric referrals) and information (such as clarifying which Internet sites contains patient-appropriate and scientifically correct information).

While not every FTD patient will need genetic counseling, the need to address genetics in the FTD setting has greatly increased over the past decade, with 15–30% of FTD cases being attributed to a known genetic cause and approximately 40% of patients describing a positive family history for neurodegenerative disease [4–7]. Thoroughly addressing genetic issues can often take more time than a physician's clinical schedule allows, and can raise family issues that go beyond patient care. A referral to genetic counseling can provide the patient with access to a health professional whose specific goal is to focus on their genetic issues and questions, freeing the physician to spend more time on appropriate care and management of the patient. In the case of Mr. G., it was the combination of skills and evaluations by the neurologist and genetic counselor together that defined the need to discuss FTD genetics with the patient and provided Mr. G. and his family with a high level of care, education, and support. As research continues to uncover genetic causes and risk factors for FTD and other neurodegenerative diseases, it will be important for clinicians to have established relationships with genetic counselors in their geographic area [8] (www.nsgc.org).

Case 2

Mr. B. is a 65-year-old man with a two-year history of memory complaints and unsteadiness. He had recently retired from his job as a college professor because of trouble organizing his lectures. Additionally, his wife complained that when watching TV, he felt that the TV characters were in the room. Mrs. B. began to worry that he was depressed or psychotic, and shared her feelings with the primary care physician. After an examination, Mr. B. was referred to a neurologist. A neurologic and neuropsychological evaluation concluded that Mr. B. met criteria for dementia, with deficits in memory, visuospatial, and executive function. Additionally he was found to have mild rigidity, ataxia, and dysarthria. An MRI showed global atrophy with mild cerebellar and thalamic atrophy. Because Mr. B.'s sister had recently been diagnosed with ALS, the neurologist ordered an EMG, which was normal. Because of the memory deficits, psychological symptoms, blunted affect, and rigidity, the diagnosis of dementia with Lewy bodies (DLB) was given. Over the next six months, Mr. B. began exhibiting more agitation and paranoia. His speech became extremely perseverative, and he insisted on a strict schedule.

Mr. B.'s niece, Barbara, is newly married and wants to get pregnant. She is concerned about her family history of ALS. Not only had her mother been recently diagnosed at age 61, but also her maternal grandmother died of ALS at age 59. Barbara locates a genetic counselor specializing in neurogenetics by consulting <http://www.nsgc.org>, and makes an appointment to discuss her options. Barbara and her husband, Rich, come to the appointment. The counselor takes an extensive family history, noting the two cases of ALS. She asks if anyone else in the family has had any neurologic or psychiatric condition. Barbara responds that her uncle

has some kind of dementia and something to do with PD. She also mentions that her 35-year-old first cousin, daughter of this uncle, has recently been hospitalized for a psychotic break. This cousin had always been normal until this nervous breakdown. Barbara thinks that her father's illness might have precipitated her condition. Barbara's father is living and well, as are her older brother and younger sister. Barbara's uncle has a healthy 32-year-old son in addition to his daughter.

The genetic counselor discusses the genetics of ALS and says that two generations of first-degree relatives with the disease is concerning. She also mentions that the uncle's condition could possibly be related. Barbara asks if she could be tested for the ALS genes. The genetic counselor explains that an affected family member would need to be tested first in order to make Barbara's test meaningful. She explains that hereditary ALS could be caused by mutations in many genes, and not all genes are known. If a mutation is found in an affected person, then predictive testing could be performed for that mutation. Without knowing the family mutation, a negative result on predictive testing would be meaningless because a mutation could still exist in some unknown or untested gene. The counselor also discusses autosomal dominant inheritance and how finding a mutation in Barbara's mother would put her at 50% risk for inheriting that mutation. If she harbors the mutation, she would most likely develop the disease and she would have a 50% risk of passing it to her children. However, discovering the gene in the family would also give the couple information needed for reproductive options. She explains that Barbara could elect to have predictive testing. If she has the mutation, the couple could decide not to have children, proceed with a pregnancy without testing,

adopt, have an egg donor, have prenatal testing, or have pre-implantation genetic diagnosis (PGD). Through in vitro fertilization followed by PGD, embryos would be tested, and only those embryos lacking the family mutation would be implanted. She also says that it would be possible to do non-disclosing PGD should Barbara want to prevent transmission of the gene to offspring while not knowing her own genetic status.

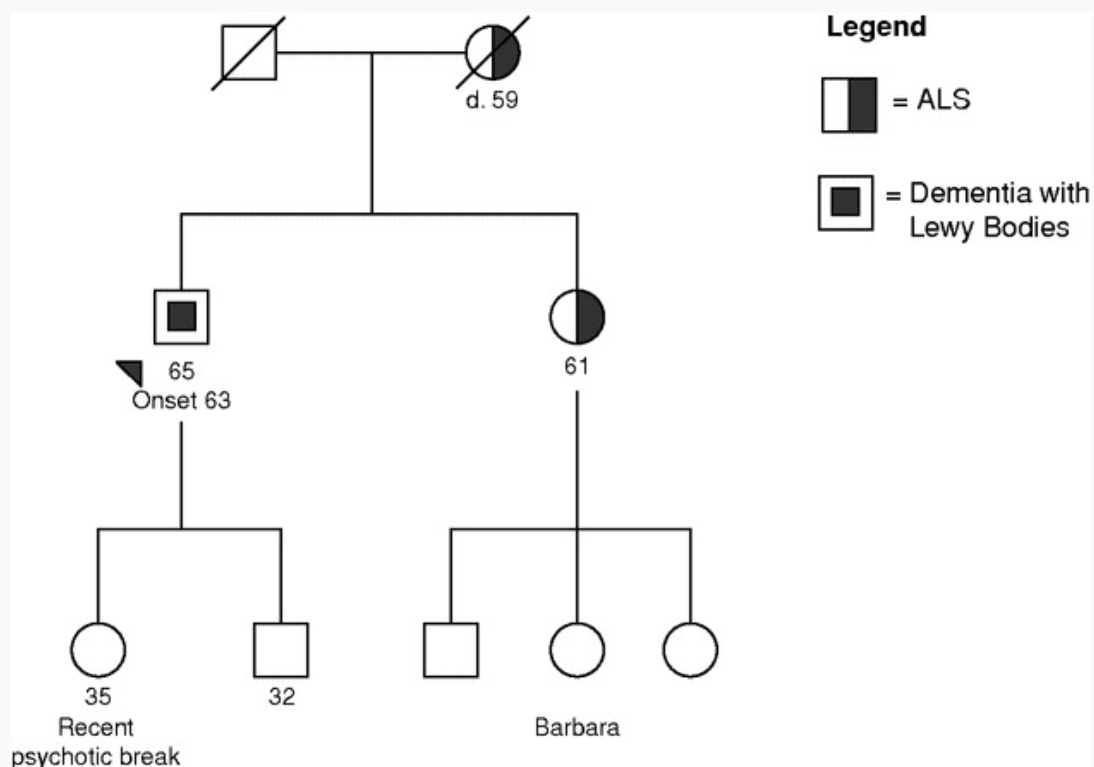


Figure 12.2 Pedigree for Case 2.

The counselor points out that although Barbara can learn her own status if she wishes, if her result comes back positive for the mutation, she could not be told exactly when or what symptoms would develop. She might develop symptoms at an earlier or later age than her mother or uncle. Additionally, if she wants predictive testing, she should first obtain any insurance that she would want for the future. Although the federal Genetic Information Non-

discrimination Act (GINA) protects against discrimination based on a hereditary family history for health insurance and employment, it does not cover long-term care insurance, life insurance, or disability insurance. If positive, Barbara could have a hard time obtaining these. Barbara said that she would talk with her parents and siblings. She is not sure that her brother would want to know about the possibility of a hereditary condition as he already has two children.

Barbara calls the counselor two weeks later to report that her parents have agreed to testing. Her sister agrees that the information is important. Her brother said that he would not want to test himself should a mutation be found, but would not deprive his sisters of their right to know. The family arranges with their neurologist to have a family counseling session followed by a blood draw. Because the family history includes both ALS and dementia, genetic testing for *C9orf72* is ordered first with reflex testing to the rest of the ALS genetic panel. Results demonstrate a hexanucleotide repeat expansion in the *C9orf72* gene in Barbara's mother. At a meeting with both the neurologist and genetic counselor, this result is given to the patient, her husband, and their two daughters. The genetic counselor explains the meaning of this expansion and what is known and not known about its effect. She recounts how the gene displays autosomal dominant inheritance with high penetrance, but that the exact penetrance is not yet known. She also explains that the gene expansion could result in various phenotypes. She mentions that although behavioral variant FTD is the most common presentation of *C9orf72*-associated FTD, memory complaints and psychotic symptoms are not unusual. When Barbara asks if this information

should be given to her aunt, the genetic counselor says she thinks it would be a good idea and offers to speak with her if she wishes.

Barbara schedules an appointment for predictive testing counseling. She understands that the protocol for predictive testing follows the Huntington's disease (HD) protocol. She would have another counseling session with her husband to consider the impact of testing on each of them, Barbara's family, and their future children. She would then undergo a neurologic examination to rule out early symptoms and a psychological evaluation to assess her mental status and ability to cope with results. Following testing, she would return for in-person results with her husband. If positive, they would be referred to an infertility center familiar with PGD.

Later that week, the genetic counselor receives a call from Barbara's aunt, Mrs. B., requesting an appointment. Mrs. B. and the genetic counselor discuss the possibility of *C9orf72* testing for Mr. B. Mrs. B.'s greatest concern is keeping the information from her psychotic daughter. She is in recovery and Mrs. B. is terrified that the information could make her worse. Mrs. B. doubts that her daughter will ever have children and, therefore, the information would not be helpful. She refuses to consider that her daughter's symptoms might be related to the gene. The counselor asks about her son. She says that her son might be interested, but that if he knew, it would be hard to keep the information from his sister. The counselor acknowledges that family secrets are difficult and suggests that she speak to her son and plan together.

Mrs. B. calls back to say the neurologist is arranging testing. The test reveals that Mr. B. has the *C9orf72* expansion. The counselor offers to meet with Mrs. B.'s son any time in the future.

Mr. B.'s case history highlights several aspects of genetic counseling for FTD, as well as specific counseling about the *C9orf72* hexanucleotide expansion. Once again a complete family history reveals clues to the pathogenic mutation in the family. The presence of dementia in a family with ALS was enough to raise the possibility of *C9orf72*, especially since psychosis was noted. This case also shows the importance of testing an affected person before predictive testing. For example, testing Barbara for *SOD1* would have been meaningless. She would have been negative, but she would not have been tested for the family's causal gene. The variable phenotype of *C9orf72* expansion carriers is also underscored in this case. Genetic testing will predict the high probability of developing symptoms, but which symptoms and when they will develop cannot be predicted. Even though Barbara could prevent the expansion from passing to her child, her onset could be earlier than that of her mother and uncle, and might interfere with her ability to parent. This possibility needs to be explored in presymptomatic genetic counseling. Presymptomatic testing should also address obtaining insurance before the test.

What if no affected family members was willing to have genetic testing? This situation is extremely difficult for the unaffected family member wanting information. Barbara could have elected to have the entire ALS panel. However, predictive testing is not covered by most insurance plans, and using insurance for this purpose is not recommended even if testing were covered. Despite GINA, raising red flags is not a good idea. If Barbara decides to pay out-of-pocket, the cost of the panel may be prohibitive. And even if she goes ahead, results may be uninterpretable. A positive result in any gene would mean that she will develop symptoms at some point. A negative result would mean that she does not carry any of these genes but that there is no guarantee that the family gene had been tested. Worse yet would be a result of unknown significance. In this case, a

variant would be found in one of Barbara's genes. Since an affected person was not tested, the meaning of this variant would be unknown. In fact, even when an affected person is found to have a variant, unless the variant can be shown to segregate with the disease in the family, its meaning is equivocal. When affected family members refuse testing, they may be willing to bank DNA in a commercial DNA bank or to have an autopsy, which not only provides definitive diagnosis, but also provides tissue for future DNA testing.

The case also points out the family dilemmas that emerge during the genetic counseling process. Mrs. B. would not share genetic information with her daughter. This decision is entirely understandable because of her concerns for exacerbating her daughter's psychological state. At the same time, her daughter's symptoms might be a precursor to the disease, and if so, sharing the information with her daughter's doctors could be beneficial. Moreover the existence of a genetic family secret is problematic. Even a friendly family gathering might result in a slip of the tongue. Once again through anticipatory guidance, genetic counseling can help a family proactively plan whether and how to pass on information. Much of the time, having an open discussion prior to testing can determine who wants or does not want the information.

Case 3

A local neurologist contacts a genetic counselor. The neurologist followed a female patient with a rapidly progressive dementia and movement disorder. The patient recently died at age 45 and a brain autopsy was performed. The autopsy result was FTD with significant tau pathology. Based on these findings, the patient's husband was told that a *MAPT* mutation might be responsible, and

genetic testing was ordered using DNA from brain tissue. The result was positive for a known mutation and the result was reported back to the family. The neurologist feels the family of the deceased patient could benefit from genetic counseling to discuss the genetic results.

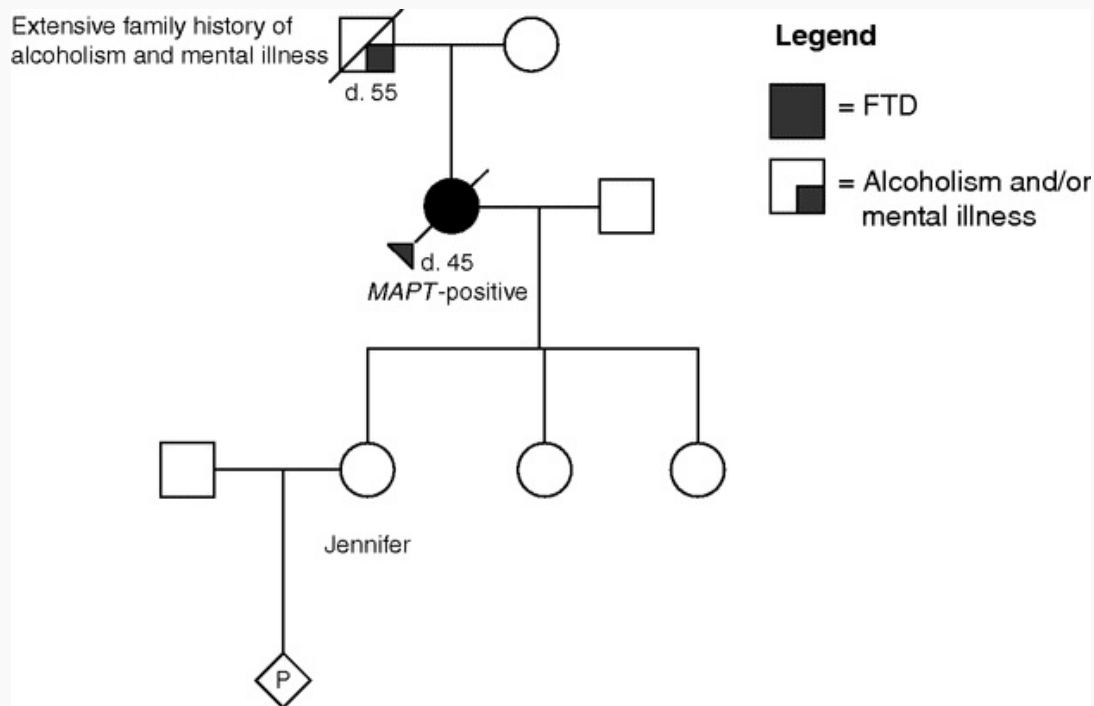


Figure 12.3 Pedigree for Case 3.

The genetic counselor meets with the husband of the deceased patient, Mr. K. Mr. K. explains that he is interested in learning anything that can help their three children, ages 22, 20, and 18. He relates that he struggled with his wife's illness, as she was the type that did “everything right.” He feels that the genetic test result has given him some closure, knowing there was nothing that could have been done to avoid the disease or save her. Mr. K. also shares that the genetic test result has had a considerable impact on the extended family of his deceased wife, as there is a high incidence of alcoholism and mental instability in her father's family. Upon

sharing what he has learned about FTD and the genetic nature of the disease with his in-laws, he feels that perhaps some of the negative stigma will be reduced in the future by accurate diagnoses and appropriate medical care.

The genetic counselor answers all of Mr. K.'s questions related to the inheritance of FTD, which leads to a discussion of his children. Mr. K. has not yet told his children about the genetic result, but feels that he will need to tell them soon. He is torn by his personal feeling of duty to inform his children about their risk, but also to protect them from the knowledge. The genetic counselor discusses Mr. K.'s concerns with him, answering his questions as they arise, and supports his plan to share the information with his daughters. The genetic counselor encourages Mr. K. to stay in touch and to share her name and contact information with any family members that may want to talk with her.

Two years later, Mr. K.'s eldest daughter, Jennifer, contacts the genetic counselor and arranges for a genetic counseling session for both herself and her fiancé, John. Jennifer and John arrive together. They share that they are pregnant; they have not told anyone about the pregnancy, as it was unplanned and they are uncertain how to proceed given the genetic risk. Jennifer becomes upset, stating that she has always feared that she would end up just like her mother, and is now sick with guilt over possibly passing the disease to her own child. She also says that she is uncertain that she and John should get married, as she does not want to burden him when she eventually develops disease. John is adamant that he does not care and wants to marry her, and reminds her that she might not even get sick like her mother did. The genetic counselor asks Jennifer and John whether they wish to review Jennifer's mother's genetic test

results together and discuss what is currently known about FTD and the *MAPT* gene. Jennifer and John agree this would be helpful. The genetic counselor reviews the genetics of FTD, the *MAPT* gene, and the specific finding in Jennifer's mother. She explains autosomal dominant inheritance, carefully answering Jennifer's specific questions about the risks to herself and her pregnancy. Jennifer and John have questions about what could be done if someone did carry the mutation, and the genetic counselor explains that there are no current preventative treatments. They discuss limitations of testing, such as not being able to predict when symptom onset would occur, or what types of symptoms someone might have. They also discuss that if Jennifer did not inherit the mutation, her risk for FTD would drop to the general population risk, and there would be no chance of the gene skipping over her and reappearing in her child. The genetic counselor reviews the option for predictive genetic testing, explaining the three-visit model that provides both pre- and post-test counseling and support. Jennifer asks about genetic testing for the pregnancy, which the counselor reviews, explaining that it is technically possible, but carries ethical considerations. The couple is visibly overwhelmed by the information, and the genetic counselor acknowledges that this is a lot of information to process. The couple agrees and says they need time to process everything they learned. The genetic counselor makes a plan to follow up with Jennifer by telephone.

The genetic counselor calls Jennifer the following week. Jennifer seems to be struggling with what is the “right” course of action for her to take. Jennifer states that while she is still worried that she will get FTD like her mother, she also feels some hope that she has a 50% chance of not inheriting the *MAPT* gene mutation. She

always assumed her risk was closer to 100%, and the reality of 50% has brought some relief. She expresses that she wants to be happy about her pregnancy and her future life with John; she feels that she is generally content with her life at this time. The genetic counselor gently asks whether Jennifer has any desire to talk more about genetic testing options, to which Jennifer says no. Jennifer says that she feels she wants to embrace her life and enjoy it, that she does not want to do any genetic testing that could impact her life plans at this time. She also does not think she wants to know if she will definitely get FTD if there is nothing she can do to prevent it. The genetic counselor supports Jennifer's decision and states that genetic testing will always be an option if Jennifer wants it. Jennifer thanks the genetic counselor for her time and says that she appreciated the support for her decision.

The impact of a genetic test result can often be felt beyond the immediate patient. This is particularly true in FTD. For the patient, the diagnosis of FTD can be a long road filled with misdiagnoses or uncertain diagnoses. Only autopsy allows a definitive diagnosis. However, for patients who carry a known pathogenic mutation in a FTD gene, the genetic test result is arguably equal to a brain autopsy by confirming the diagnosis of FTD. Although substantiating familial risk, diagnostic confirmation can bring a sense of closure to patients and families. And while currently there are no specific FTD treatments, a positive genetic result may prevent unnecessary care, such as further testing or treatment for the wrong disease. It is hopeful that in the future, FTD-specific medications will be available, and genetic testing may help identify those individuals who are most likely to benefit from a certain therapy. A positive result may also provide

information to the clinician regarding the pathology of the disease, which in turn could inform discussions regarding clinical issues, such as prognosis.

As seen in the case example, the discovery of the *MAPT* mutation provided closure to Mr. K. by giving a reason for his wife's illness. This desire to understand the cause of FTD is understandable and common, and in some cases, genetic testing may provide the answer to the question of “why?” However, care must be taken to explain that a negative test result does not mean that FTD is the wrong diagnosis; a negative genetic test result neither proves nor disproves the clinical diagnosis. It is specific to the FTD gene or genes that were tested. Other unidentified pathogenic genes or risk factors for FTD could play a role, or perhaps the diagnosis is incorrect and other genes are responsible. Families with positive family histories but negative genetic testing may benefit from participating in genetic research studies to further define the genetic contributions to FTD.

Three possible results of genetic testing may be reported: positive, negative, and variant of unknown significance (VUS). For *C9orf72* testing, the possible results only differ in that hexanucleotide repeat expansion can be positive (expansion correlated with pathogenic status), negative (within accepted normal range of size), or an intermediate length that has not yet been clearly defined. The clinical report issued for any genetic test result should provide documentation of how the raw data were analyzed and interpreted, including an explanation of how a positive, negative, VUS, or intermediate *C9orf72* result is defined by that particular laboratory. The interpretation of a VUS can be difficult for health professionals, let alone patients, to understand. Some laboratories or research centers may be willing to test additional family members in an attempt to define whether or not the VUS segregates with disease. The unknown nature of either a VUS or intermediate *C9orf72* expansion can be a source of confusion and distress for patients and families; having an ongoing relationship with a genetic

counselor to discuss the result, interpret it in view of family history information, and discuss research updates may be beneficial.

Uncovering a known, pathogenic FTD gene mutation in a patient can have an immediate impact on the family. The first individual in the family who learns of an inherited risk can inadvertently become the messenger of the news for other relatives. Genetic counseling can help individuals discuss strategies for sharing the information with immediate and extended relatives. In some families, learning of a genetic cause for the disease may bring a sense of relief, providing medical proof and facts about a recognized familial disease. By giving a scientific reason for a complicated family history, stigma may be reduced, as seen in the case example. In other families, the detection of a genetic cause may bring concerns for future stigma. Feelings of fear or guilt for the next generation may be caused by a positive genetic test result. These feelings are common in many genetic conditions, not just FTD, and genetic counseling plays an important role in helping individuals and families adapt to the familial and psychological impacts of learning genetic information.

The detection of an FTD gene mutation further impacts a family by defining the risk to blood relatives. At this time, all known FTD genes have autosomal dominant inheritance, conveying a 50% mutation risk to first-degree relatives. Thus any future relative's genetic test result will be definitively positive or negative. The potential exception to this rule is *C9orf72* intermediate expansions because of the possibility of repeat length instability and anticipation. Documentation of the known family mutation or expansion results should be provided to help guide explanation of the possible testing outcomes. If an individual tests negative for a known family FTD gene mutation, they have not inherited the mutation and their lifetime risk of disease drops to the general population risk. The risk of passing the mutation to offspring is eliminated. A positive result, however, confers a

50% risk of passing the gene mutation to any offspring. The penetrance of disease and possible genotype–phenotype correlations can differ by gene and sometimes by specific mutation, which is another reason for careful pre-test consideration of all known data regarding the family mutation.

While greater emphasis is typically put on the impact of a positive result, a negative result can also impact family members. A negative genetic test result may provide reassurance to the siblings and children of a patient with FTD. However, a negative result should be carefully interpreted in light of a family history suggestive of a hereditary pattern of disease. In such cases, further clinical genetic testing of genes associated with non-FTD diagnoses, genetic research studies, and DNA banking should be discussed. If no genetic cause has been identified in the family, there is no need to consider presymptomatic testing in family members. This again echoes the importance of first testing a patient affected by the disease in order to establish the presence (or absence) of a genetic cause.

Once a causal gene mutation has been uncovered, other family members are candidates for predictive genetic testing. The process and theories behind this testing process were first defined in HD. Most centers that provide predictive genetic testing for adult-onset neurodegenerative conditions, such as FTD, will use a model that is shaped by the guidelines and literature published on HD [9]. The decision to pursue predictive genetic testing is a highly personal one; even within families, varied opinions and outlooks on the value of learning one's genetic status can exist. At this time, there is no medical benefit and no prevention that can be offered to those individuals who learn they carry an FTD-causing gene mutation. Some individuals may see the information as having personal benefits, such as helping life and family planning decisions, or by providing relief from uncertainty and distress. However, still others will see no benefit in testing, which is an equally sound decision. In the case example,

Jennifer decided against predictive genetic testing; she was comfortable living with her 50% risk. The process of predictive genetic testing is intended to provide a thorough and supportive approach to the genetic testing decision. It is important that the individual has weighed all the pros and cons, considered all the possible testing outcomes and impacts, and explored and challenged their personal testing decision, with the end result being a well-informed, realistic, and confident final decision. The value of genetic counseling in predictive genetic testing is immense. As FTD is an adult-onset condition, predictive genetic testing for children (individuals younger than 18 years old) is not advised. It is recommended that individual autonomy be respected, giving each individual the right to decide whether or not they desire to know their personal genetic information. This carries over into ethical considerations of prenatal testing for a condition such as FTD, as prenatal testing is essentially testing a minor. Besides respecting autonomy, there is also the concern that a child that grows into adulthood knowing such significant information could be at risk for unknown psychological effects, as well as a risk for genetic discrimination.

Conclusions

As shown by the previous case histories, genetic counseling for FTD is quite complex. Physicians should encourage anyone with a possible family history of FTD or FTD-ALS to have genetic counseling. Additionally, people who worry about the possibility of hereditary FTD can benefit from counseling. Often, talking through their family history and providing information can reduce anxiety. Importantly, patients should understand that going for genetic counseling in no way commits them to genetic testing.

The process of genetic counseling helps patients understand the likelihood of finding a mutation in one of the FTD genes. Additionally, it helps identify the appropriate family member to test. If a healthy individual is interested in predictive testing, an affected family member should be tested first. If an affected family member is unwilling to be tested, the genetic counselor can help the family explore further options such as DNA banking for future testing or brain donation which will provide definitive diagnosis and tissue for testing.

The heterogeneity of FTD can make genetic testing complicated and costly. In some cases, symptoms, autopsy, and family history can guide genetic testing. For example, any family history of ALS should imply initial testing of *C9orf72* with reflex testing for *MAPT* and *GRN*. Several algorithms have been designed to assist with testing strategies [7, 10–12].

Genetic testing has benefits, risks, and limitations. The major benefits of diagnostic testing are to obtain a definitive diagnosis and information for the family. Predictive testing can allow the individual to plan for the future and to have specific reproductive options, especially PGD. At the same time, genetic testing poses risks. Learning that one carries a mutation can result in guilt for the carrier who may have passed the gene to children, as well as depression and anxiety, particularly in presymptomatic testing. Pre-test genetic counseling allows for anticipatory guidance about possible negative feelings as well as the potential impact on one's life; it encourages the individual to think about worst case scenarios, impact on themselves, their partners, and their family members, mechanisms for communication, and implications for insurance.

Patients also need to be informed about the limitations of genetic testing. As stated above, before predictive testing is possible, a mutation should be found in an affected family member. Although the discovery of a mutation in an unaffected person would certainly be definitive, a negative

result in the absence of a known family mutation could be either a true or false negative – there would be no way of knowing whether testing was performed on the causal gene. Lastly, all patients, whether symptomatic or not, must be aware that testing can reveal variants of unknown significance. Without confirmation that these variants are causal, predictive testing cannot be done.

The genetics of FTD has become much more complex. New genetic technologies are likely to add to this complexity through the discovery of new genes, especially risk loci. As clinical trials become available, the importance of knowing one's genetic status will increase. Drug trials will be steered toward specific pathologic variants that result from various genetic mutations. Medical teams need to be prepared to provide their patients with genetic information and informed choices. Genetic counseling will be essential for this process.

References

1. National Society of Genetic Counselors' Definition Task Force, Resta R, Biesecker BB, Bennett RL, *et al.* A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns* 2006;**15**(2):77–83.

2. Goldman JS, Farmer JM, Van Deerlin VM, *et al.* Frontotemporal dementia: genetics and genetic counseling dilemmas. *Neurologist* 2004;**10**(5):227–34.

3. McCarty-Wood E. The role of genetics: a piece in the FTD puzzle. In Radin G, Radin L, eds. *What If It's Not Alzheimer's? A Caregivers Guide to Dementia*, 3rd edn. Amherst, NY: Prometheus Books. 2014; 62–79.

4. Goldman JS, Farmer JM, Wood EM, *et al.* Comparison of family histories in

FTLD subtypes and related tauopathies. *Neurology* 2005;**65**(11):1817–19.

5. Rohrer JD, Guerreiro R, Vandrovcsa J, *et al.* The heritability and genetics of frontotemporal lobar degeneration. *Neurology* 2009;**73**(18):1451–6.

6. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;**72**(2):245–56.

7. Wood EM, Falcone D, Suh E, *et al.* Development and validation of pedigree classification criteria for frontotemporal lobar degeneration. *JAMA Neurol* 2013;**70**(11):1411–17.

8. Hahn SE. Primer on genetic counselling. *Continuum (Minneap Minn.)* 2011;**17**(2 Neurogenetics):268–79.

9. International Huntington Association and World Federation of Neurology. International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. *J Med Genet* 1994;**31**(7):555–9.

10. Le Ber I, Camuzat A, Guillot-Noel L, *et al.* *C9ORF72* repeat expansions in the frontotemporal dementias spectrum of diseases: a flow-chart for genetic testing. *J Alzheimers Dis* 2013;**34**(2):485–99.

11. Van Langenhove T, van der Zee J, Gijselinck I, *et al.* Distinct clinical characteristics of *C9orf72* expansion carriers compared with *GRN*, *MAPT*, and nonmutation carriers in a Flanders-Belgian FTL D cohort. *JAMA Neurol* 2013;**70**(3):365–73.

12. Goldman JS, Rademakers R, Huey ED, *et al.* An algorithm for genetic testing of frontotemporal lobar degeneration. *Neurology* 2011;**76**(5):475–8.

Section 4



Pathology and pathophysiology

Chapter 13

Neuropathology of frontotemporal dementia and related disorders



Manuela Neumann, Gabor G. Kovacs, and Ian R. A. Mackenzie

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

As discussed elsewhere in this book, frontotemporal dementia (FTD) is a clinical syndrome characterized by progressive changes in behavior, personality, and/or language, with relative preservation of memory. Major clinical subtypes include the behavioral variant (bvFTD) and two forms of primary progressive aphasia (PPA): progressive non-fluent aphasia (PNFA) and semantic dementia (SD). FTD is often associated with an extrapyramidal movement disorder (atypical parkinsonism or corticobasal syndrome [CBS]) or with motor neuron disease (MND). A family history of FTD is present in 25–50%, indicating a significant genetic influence. Autosomal dominant FTD may be caused by mutations in several genes,

including those encoding the microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), chromosome 9 open reading frame 72 (*C9orf72*), valosin-containing protein (*VCP*), and charged multivesicular body protein 2B (*CHMP2B*) [1].

Considering the variability in clinical features and associated genetic abnormalities, it is not surprising that the neuropathology underlying clinical FTD is also heterogeneous. Relatively selective degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration, FTLD) is a consistent feature, which correlates with the main clinical manifestations. As with many other neurodegenerative conditions, the pathology of most cases of FTD includes the presence of abnormal intracellular protein accumulations. Traditionally, these inclusion bodies were demonstrated with special histochemical staining techniques, such as silver impregnation methods. Eponymous and syndromic names were used for clinical syndromes associated with a specific morphology and anatomical distribution of cellular inclusions. However, in many cases, these clinicopathologic correlations turned out to be imperfect. Modern laboratory techniques, such as immunohistochemistry, have allowed the biochemical composition of the pathologic changes to be more readily determined. In this review, we will employ the molecular-based system of nosology and nomenclature recommended in recent consensus papers [2, 3]. The term FTLD will be used as the general terminology for pathologic conditions that predominantly or commonly present with clinical FTD and major subdivisions will be designated by the protein abnormality that is presumed to be pathogenic or most characteristic (Table 13.1). Cases are further subclassified, using traditional terminology, to define specific patterns of pathology.

Table 13.1 Molecular classification of FTLD with genetic and clinical

correlations

Major molecular class	Pathologic subtype ^{u}	Associated genes	Clinical phenotypes				
			bvFTD	PNFA	SD	Park	MNI
FTLD-tau		• <i>MAPT</i>	+	(+)	(+)	+	ALS, PLS
	• PiD		+	+	+	(+)	
	• CBD		+	+		+	PLS
	• PSP		+	+		+	PLS
	• GGT		+			+	PLS
	• AGD		(+)				
FTLD- TDP		• (<i>TARDBP</i>)	(+)			+	ALS
	• Type A	• <i>GRN</i>	+	+		+	
	• Type B	• <i>C9orf72</i>	+	+	(+)	+	ALS
	• Type C		+		(+) +		
	• Type D	• <i>VCP</i>	+			(+)	ALS
FTLD- FET		• (<i>FUS</i>)	(+)				ALS
	• aFTLD-U		+				
	• NIFID		+			+	PLS
	• BIBD		+			+	ALS

FTLD-UPS	• FTD-3	•	+	(+)	(ALS)
		<i>CHMP2B</i>			
FTLD-ni			+		

^a Indicates the characteristic pattern of pathology, not the clinical syndrome.

aFTLD-U = atypical frontotemporal lobar degeneration with ubiquitinated inclusions, AGD = argyrophilic grain disease, ALS = amyotrophic lateral sclerosis, BIBD = basophilic inclusion body disease, bvFTD = behavioral variant FTD, *C9orf72* = chromosome 9 open reading frame 72 gene, CBD = corticobasal degeneration, *CHMP2B* = charged multivesicular body protein 2B gene, FET = fused in sarcoma, Ewing's sarcoma, TATA-binding protein-associated factor 15 (FUS/EWS/TAF15) family of proteins, FTD = frontotemporal dementia, FTD-3 = FTD linked to chromosome 3, FTLD = frontotemporal lobar degeneration, *FUS* = fused in sarcoma gene, GGT = globular glial tauopathy, *GRN* = progranulin gene, *MAPT* = microtubule-associated protein tau gene, MND = motor neuron disease, ni = no inclusions, NIFID = neuronal intermediate filament inclusion disease, park = parkinsonism = PiD = Pick's disease, PLS = primary lateral sclerosis, PNFA = progressive non-fluent aphasia, PSP = progressive supranuclear palsy, SD = semantic dementia, *TARDBP* = transactive response DNA-binding protein gene, TDP = transactive response DNA-binding protein, UPS = ubiquitin proteasome system, *VCP* = valosin-containing protein gene.

(+) rare cause or unusual phenotype.

FTLD-tau

A diverse group of neurodegenerative disorders, with overlapping clinical phenotypes, share the predominant pathologic feature of accumulation of abnormal forms of tau protein in neurons and glia. These “tauopathies”

include a number of sporadic and inherited conditions that commonly present with FTD, either in a pure form or as part of a more complex clinical syndrome that often includes atypical parkinsonism, and are thus grouped together within the broad pathologic designation of FTLD-tau ([Table 13.1](#)). Although estimates vary among studies, FTLD-tau is found to be the underlying pathology in approximately 40% of FTD ([Figure 13.1](#)).

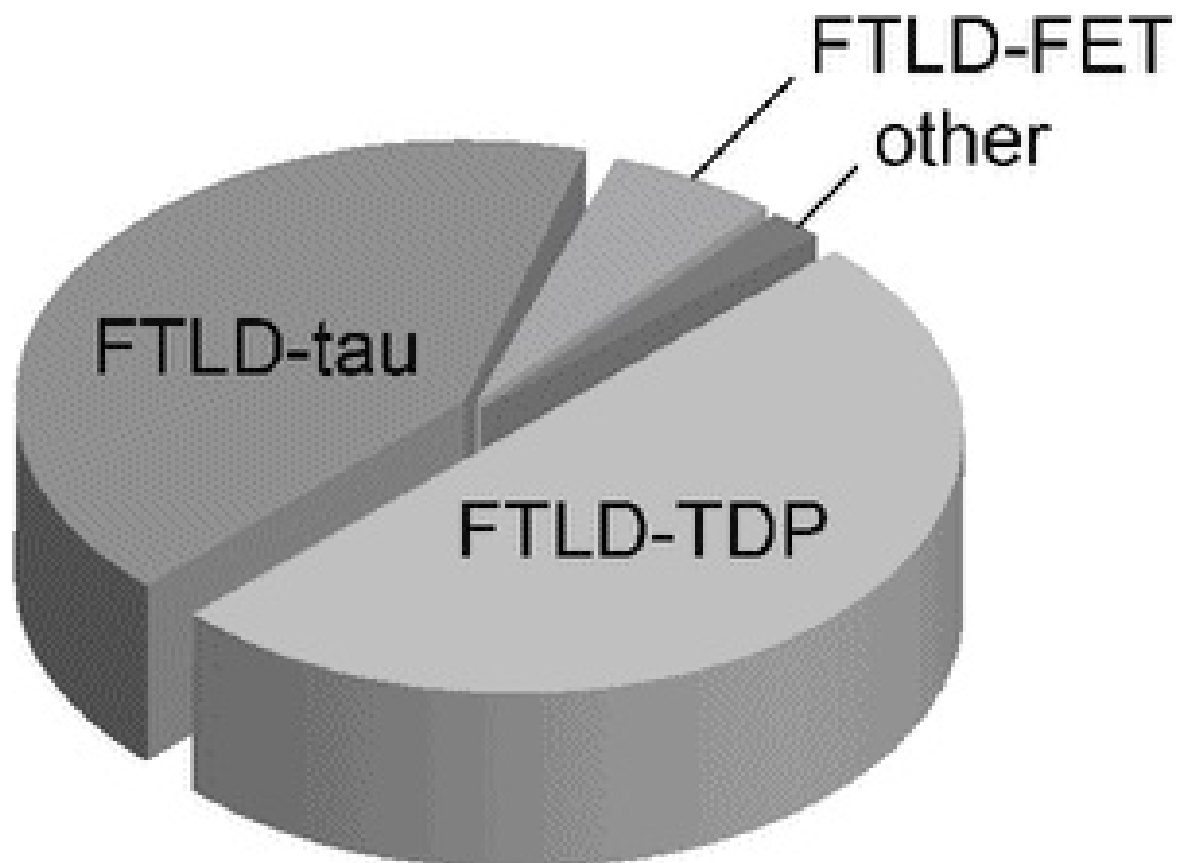


Figure 13.1 Relative frequency of major molecular pathologic subtypes of frontotemporal lobar degeneration (FTLD). FET, fused in sarcoma, Ewing's sarcoma, TATA-binding protein-associated factor 15 family of proteins; tau, microtubule-associated protein tau; TDP, transactive response DNA-binding protein.

Normal tau expression and function

Tau is a microtubule-associated protein that binds to and stabilizes microtubules and promotes their polymerization [4]. It is expressed predominantly in axons but also at low levels in glial cells. Tau plays an important role in maintaining neuronal integrity and axonal transport. The *MAPT* gene is located on chromosome 17q21 and has 16 exons (Figure 13.2A). In the adult human brain, six tau isoforms, ranging from 352 to 441 amino acids, are expressed as a result of alternative splicing of exons 2, 3, and 10 [5, 6]. These isoforms differ from one another by the presence or absence of 29- or 58-amino acid inserts in the N-terminal, and by the presence of either 3 or 4 tandem repeat sequences of 31 or 32 amino acids (3R and 4R tau, respectively) (Figure 13.2A). The repeat regions are the binding domains that mediate the interaction between tau and microtubules. Evidence that tau is more than a microtubule-associated protein comes from observations of other localizations, including the nucleus, plasma membrane, and extracellularly where it interacts with muscarinic receptors. In addition, tau has been found to have a role in cell signaling by interacting with a number of signal transduction proteins [7].

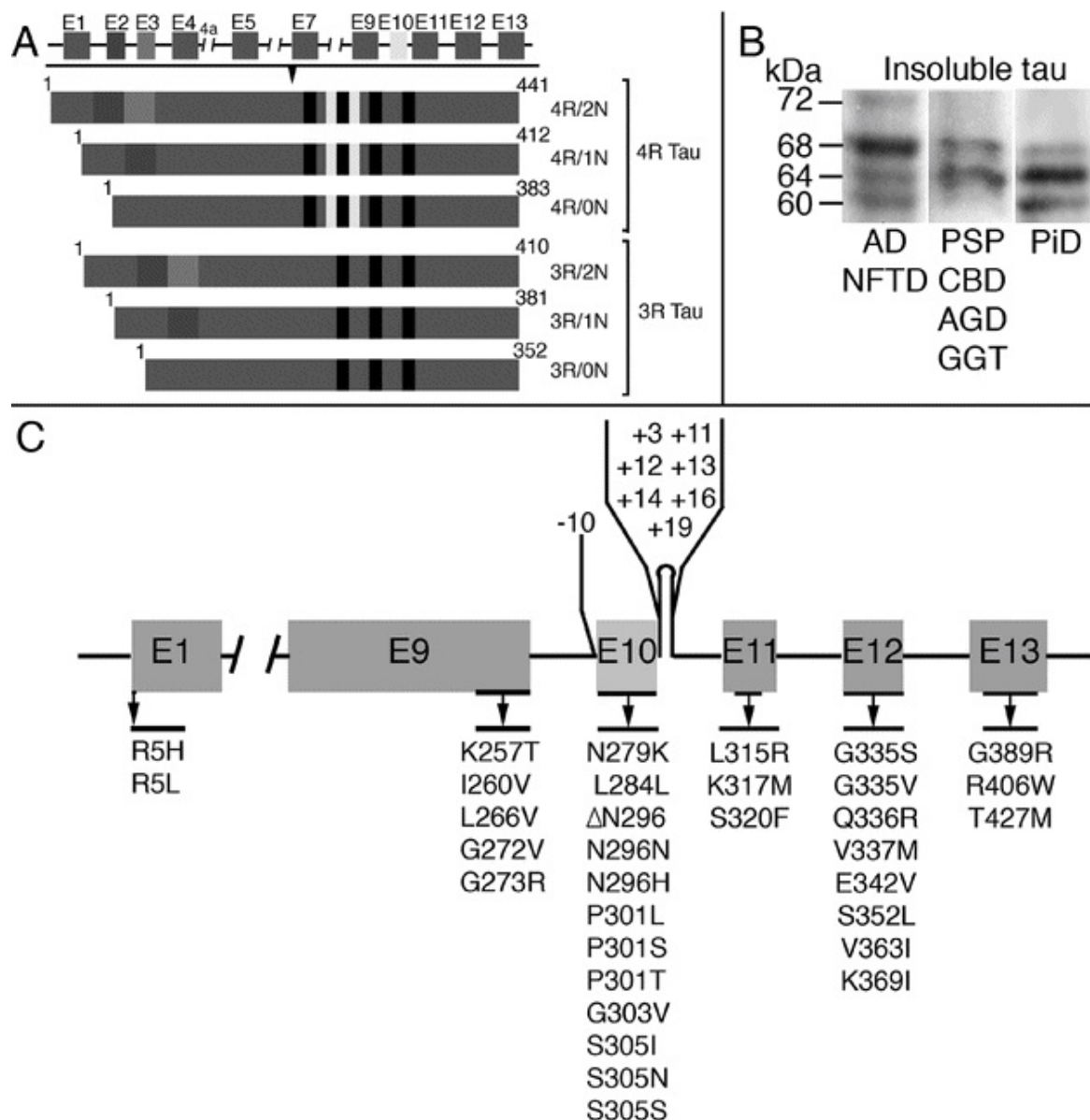


Figure 13.2 *MAPT* gene, tau isoforms, and *MAPT* mutations. **(A)** Schematic representation of the human *MAPT* gene and the six tau isoforms. The constitutively spliced exons are E1, E4, E5, E7, E9, E11, E12, and E13. Alternative splicing of exons 2, 3, and 10 give rise to six isoforms (352–441 amino acids). Alternate splicing of exon 10 results in isoforms with either 3 or 4 repeat regions which correspond to the microtubule-binding domains (3R and 4R tau, respectively). **(B)** Pathologic tau proteins revealed by Western blotting using phospho-dependent tau antibody AT8 in brain tissue from patients affected by different tauopathies. Three different electrophoretic patterns of pathologic tau proteins are illustrated. Pathologic tau bands at 60, 64, 68, and 72 kDa, corresponding to all 6 tau isoforms, are seen in

Alzheimer's disease (AD) and neurofibrillary tangle-only dementia (NFTD). Two major bands at 64 and 68 kDa, representing the 4R tau isoforms, are observed in progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), and globular glial tauopathies (GGT). Prominent bands at 60 and 64 kDa are seen in Pick's disease (PiD), indicating pathologic tau composed predominantly of 3R isoforms. Cases with *MAPT* mutations can show all banding patterns, depending on the mutation. (C) Mutations in the *MAPT* gene in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17 *MAPT*).

Tau in disease

In the normal adult human brain, similar levels of the 3R and 4R tau isoforms are expressed. Tauopathies are heterogeneous at a biochemical level, with the pathologic form of the protein differing in the relative amounts of 3R versus 4R isoforms [7]. These differences may be demonstrated by immunohistochemistry using 3R- and 4R-specific antibodies and by different banding patterns seen on Western blot analysis of insoluble protein fractions from brain tissue (Figure 13.2B). Diseases in which abnormal forms of both 3R and 4R tau accumulate (e.g., Alzheimer's disease, AD) have major bands at 60, 64, and 68 kDa, whereas those in which the insoluble protein is composed predominantly of 3R tau only have bands at 60 and 64 kDa and 4R tauopathies only have 64 and 68 kDa bands.

The most studied post-translational modification of tau is phosphorylation, which physiologically regulates its activity and microtubule binding [8]. Tau is normally phosphorylated at 2 or 3 residues, whereas pathologic forms of tau are phosphorylated at 8 to 12 residues, or more. Hyperphosphorylation causes conformational changes and promotes the assembly of tau into abnormal filaments, which adversely affect its interaction with other proteins, and thus has an impact on microtubule

stability and axonal transport, dendritic positioning and synaptic health, cell signaling at plasma membranes, protection of DNA from cell stressors, and cellular release of tau [9].

Mutations in the *MAPT* gene cause autosomal dominantly inherited neurodegenerative disease associated with the intracellular accumulation of soluble and insoluble hyperphosphorylated tau protein (see below). More than 40 mutations have been identified to date ([Figure 13.2C](#)) (<http://www.molgen.ua.ac.be/FTDMutations/>). Mutations either have a primary effect at the protein level or they affect the alternative splicing of tau pre-mRNA [6]. Mutations localized in the microtubule-binding region of tau alter the tau–microtubule interaction and may also have a pro-fibrillogenic effect, while those that affect the alternative splicing of exon 10 lead to an overproduction of 4R isoforms [10].

MAPT is located in a complex genomic region surrounded by three homologous low-copy repeats. A 900 kb genetically balanced inversion in the *MAPT* genomic region results in two extended haplotypes, H1 and H2 [11]. Inheritance of the H1 haplotype and the H1/H1 genotype is a recognized risk factor for progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [11]. The H1c sub-haplotype confers additional risk for PSP which may be due to increased tau expression, particularly of the 4R isoforms [12].

Neuropathologic subtypes of FTLD-tau

Pick's disease

The use of the term has changed over the years, but the designation of Pick's disease (PiD) is now usually restricted to cases in which the pathology is characterized by classical Pick bodies (see below). The clinical presentation is most often bvFTD or PNFA, with SD being somewhat less

common. Rare cases present with an AD-like amnesic syndrome and motor deficits are less common than in most other FTLT subtypes. The typical gross pathology is severe circumscribed frontal and anterior temporal lobar atrophy, which may be asymmetric. Non-specific microscopic features of chronic degeneration, including neuronal loss, gliosis, and swollen neurons (sometimes referred to as Pick cells) are most severe in the frontal and temporal neocortices and limbic cortex, with variable involvement of the striatum and thalamus and relative sparing of the brainstem and cerebellum. The key diagnostic feature is the presence of large, well-demarcated, round or oval neuronal cytoplasmic inclusions that are lightly basophilic, argyrophilic (with Bielschowsky and Bodian but not Gallyas silver stains), and tau-immunoreactive. These Pick bodies are always numerous in the dentate granule cells ([Figure 13.3A](#)) and CA1 pyramidal neurons of the hippocampus and are consistently present in affected regions of neocortex [13]. They may also be found in lesser numbers in many subcortical regions. Pick bodies are largely or exclusively composed of 3R tau. Glial tau pathology is less abundant than in other FTLT-tau subtypes, and is represented by ramified astrocytes and tiny globular inclusions in oligodendrocytes.

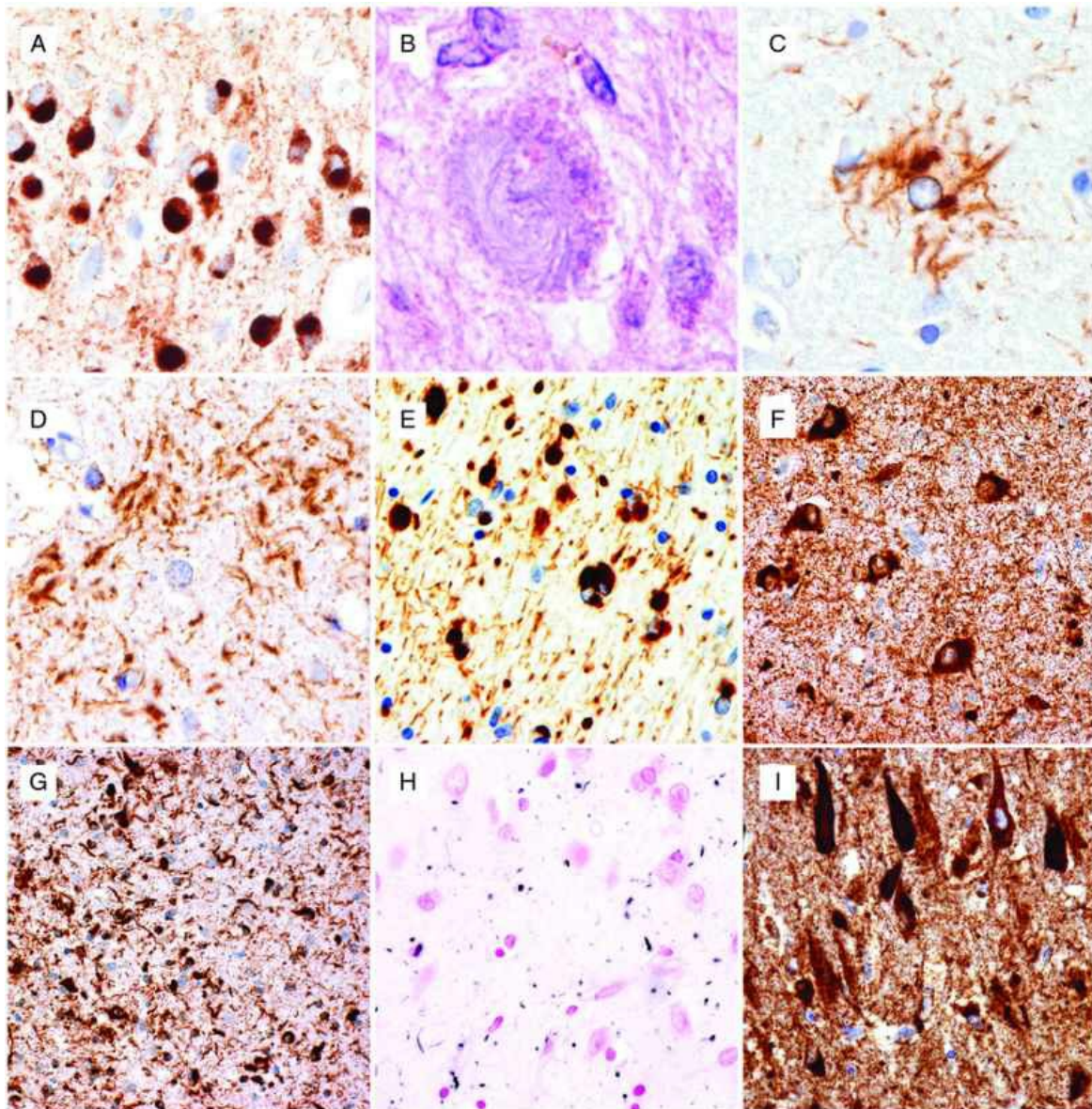


Figure 13.3 Neuropathologic features of tauopathies. (A) Pick bodies in dentate granule cells of the hippocampus in Pick's disease. (B) Globose neuronal tangle and (C) tufted astrocyte in progressive supranuclear palsy. (D) Astrocytic plaque in corticobasal degeneration. (E) Globular oligodendroglial inclusions in globular glial tauopathy. (F) Abundant neuronal and (G) glial inclusions in the hippocampus in a case of FTDP-17 *MAPT* with the S305I mutation. (H) Abundant grains in the hippocampal CA1 region in argyrophilic grain disease. (I) Prominent neurofibrillary degeneration in the hippocampal CA1 region in neurofibrillary tangle-predominant dementia. (A, C-G, I) immunohistochemistry using phospho-dependent tau antibody AT8, (B) hematoxylin and eosin, (H) Gallyas silver stain.

Progressive supranuclear palsy

The classic clinical presentation of PSP, known as Richardson's syndrome, includes falls, postural instability, axial rigidity, bradykinesia, slow unsteady gait, and ophthalmoplegia. Other presentations, including asymmetric parkinsonism, pure akinesia with gait freezing, CBS, bvFTD, PNFA, apraxia of speech, and primary lateral sclerosis (PLS), are also described [14]. The degree and distribution of gross cerebral atrophy varies and correlates with the predominant clinical features. There is atrophy and discoloration of a variety of subcortical regions, which may include the subthalamic nucleus, globus pallidus, midbrain tectum/tegmentum, substantia nigra, basis pontis, cerebellar dentate nucleus, and cerebellar peduncles. Neuronal and glial cytoplasmic inclusions are best demonstrated with tau immunohistochemistry and Gallyas silver stain. The most characteristic neuronal inclusions are globose neurofibrillary tangles (NFTs) which predominate in subcortical nuclei ([Figure 13.3B](#)). Flame-shaped NFTs (similar to AD) may be present in small numbers in the cerebral cortex, and diffuse granular cytoplasmic tau-immunoreactive neuronal “pre-tangles” are present in cortical and subcortical regions. Glial inclusions are present in gray and white matter and include thread-like structures, oligodendroglial coiled bodies, and thorn-shaped astrocytes. However, the most disease-specific pathologic finding is the presence of tufted astrocytes in which tau immunohistochemistry and silver stain highlights a complex branching pattern of proximal and medial cell processes ([Figure 13.3C](#)). The neuropathologic diagnosis of PSP is based on demonstrating widespread involvement of subcortical regions by these various neuronal and glial inclusions, all of which are composed primarily of 4R tau. Grumose degeneration of the dentate nucleus of the cerebellum, in which neurons are surrounded by clusters of eosinophilic granular structures

that result from the degeneration of presynaptic terminals, is a well-recognized but non-specific feature of PSP [15].

Corticobasal degeneration

The classic clinical presentation of CBD is the corticobasal syndrome, which includes asymmetric ideomotor apraxia, rigidity, dystonia, myoclonus, cortical sensory signs, and alien limb phenomenon. Additional clinical syndromes may include Richardson's syndrome, posterior cortical atrophy syndrome, bvFTD, and PNFA [16]. Cerebral atrophy is often asymmetric and focal with the distribution correlating with the clinical features. Gross atrophy of subcortical structures is usually not as widespread as in PSP, with the globus pallidus and substantia nigra most often affected. The histopathologic features of CBD overlap with those of PSP and other 4R tauopathies and are best demonstrated with tau immunohistochemistry and Gallyas silver stain. Neuronal inclusions include diffuse granular cytoplasmic tau immunoreactivity, small NFT, globose tangles (sometimes referred to as corticobasal bodies), and occasional small Pick body-like spherical inclusions. Thread-like structures tend to be abundant in the gray and white matter and there are variable numbers of oligodendroglial coiled bodies and thorn-shaped astrocytes. However, the most disease-specific type of inclusion in CBD is the astrocytic plaque, which appears as a circular or ring-shaped collection of short argyrophilic, tau-immunoreactive cell processes that bear a vague resemblance to the neuritic plaque of AD (Figure 13.3D). Unlike the tufted astrocytes of PSP, which involve the more proximal and medial cell processes, astrocytic plaques result from the accumulation of pathologic tau in the distal segments of astrocytic processes, and the associated cell body and nucleus are often not apparent. An additional pathologic feature that was stressed in early

descriptions of CBD is the presence of ballooned, achromatic neurons in the cerebral cortex [15]. These are readily apparent on hematoxylin and eosin stained sections and highlighted with immunohistochemistry for neurofilament (NF) proteins and α B-crystallin, but are only weakly argyrophilic and variably tau-positive. Although achromatic neurons may be found in limbic regions in many neurodegenerative conditions, their presence in the neocortex is diagnostically helpful but not specific for CBD.

Globular glial tauopathies

Globular glial tauopathies (GGT) is the term that has recently been recommended for a group of uncommon 4R-predominant tauopathies that are characterized by distinctive and widespread tau-positive globular glial inclusions (GGI) [17]. These cases were previously included in reports of atypical tauopathies under a variety of different terminologies, including “sporadic multiple system tauopathy with dementia.” The clinical presentations include bvFTD with or without extrapyramidal features, PLS, or a combination of FTD and PLS [17]. The distinguishing neuropathologic feature is the globular morphology of cytoplasmic inclusions that occur in both oligodendroglia and astrocytes (Figure 13.3E). While the oligodendroglial inclusions are argyrophilic with Gallyas method, the astrocytic tau deposits are generally silver-negative. Neuronal tau pathology is mainly represented by diffuse cytoplasmic immunoreactivity or globular inclusions, which are also composed primarily of the 4R isoform. Involvement of the white matter is always more prominent than in other tauopathies.

FTD and parkinsonism caused by MAPT mutations

More than 40 different *MAPT* mutations have been identified in over 100 families with an autosomal dominant inheritance of FTD and parkinsonism (FTDP-17 *MAPT*), representing approximately 10% of familial FTD cases (<http://www.molgen.ua.ac.be/FTDMutations/>). Most of the pathogenic mutations are either missense or deletions in exons 1 or 9–13 or mutations in the intron that follows exon 10. The clinical and pathologic features of FTDP-17 *MAPT* vary significantly, with some degree of correlation with the specific mutation (see below) [18]. The phenotype usually includes some combination of behavior and personality change, cognitive deficits, and atypical parkinsonism. Language deficits, pyramidal dysfunction, and other motor features may also occur but are less common. The neuropathology is characterized by neuronal and glial inclusions (Figure 13.3F–G) composed of hyperphosphorylated, filamentous tau in cortical and subcortical gray and white matter. The anatomical distribution, inclusion morphology, and biochemistry overlap with the sporadic tauopathies. In general, mutations which affect the alternate splicing of exon 10 result in a relative increase in 4R tau and are associated with neuronal and glial pathology that resembles that of sporadic 4R tauopathies (PSP and CBD). In contrast, mutations in exons 9, 11, 12, and 13 result in a predominance of neuronal inclusions; either Pick bodies associated with a 3R-predominant insoluble tau banding pattern or NFT with the same three bands as is found in AD, indicating both 3R and 4R tau isoforms.

Other tauopathies

In addition to atypical and overlapping forms of PSP and CBD, there are reports of sporadic tauopathies that do not fit into current classifications and present as FTD [13, 19]. Various terminologies have been recommended for cases with similar clinical and pathologic features; however, these

designations often overlap and are not yet widely accepted. Moreover, comprehensive studies of the aging brain have revealed complex constellations of tau pathologies that involve the frontal and temporal cortices as well as limbic and subcortical structures with various neuronal and glial inclusions, often combined with some AD pathology and even some transactive response DNA-binding protein 43 (TDP-43) proteinopathy [20].

Although argyrophilic grain disease (AGD) and NFT-dementia each rarely present with clinical features of FTD, they are worth mentioning in this context because their pathology often overlaps and may coexist with other forms of FTLD-tau. AGD is a sporadic 4R-predominant tauopathy that usually presents as a late-onset progressive dementia with relatively mild features that are similar to AD [21]. Personality and emotional changes are common but only rarely do patients present as typical bvFTD. Diffuse frontotemporal atrophy is usually mild; however, severe atrophy of the ambient gyrus is frequently documented and it is involved early in disease according to a proposed staging paradigm [22]. The key histopathologic feature is the presence of small dot-like spindle-shaped structures (grains) that are argyrophilic and immunoreactive for tau, ubiquitin, and p62 and thought to represent degenerating dendrites (Figure 13.3H). Grains are most abundant in the amygdala and limbic cortex of the mesial temporal lobe and may extend into the adjacent temporal neocortex. Additional pathologic changes that occur in affected limbic regions include oligodendroglial coiled bodies and silver-negative, tau-positive pre-tangles. Most cases of AGD also have some AD pathology, usually NFT in a Braak stage I–III distribution, and it has been suggested that the presence of argyrophilic grains may lower the threshold for AD-type dementia. A degree of argyrophilic grain pathology has also been reported in a wide variety of

other tauopathies (particularly other 4R tauopathies), non-tau-based neurodegenerative diseases, and very old non-demented subjects [21].

A subset of late-onset dementia cases, termed NFT-dementia, is found to have abundant AD-type neurofibrillary pathology (3R- and 4R-positive) that is restricted to the allocortex (Braak stage IV) (Figure 13.3I) with only minimal involvement of the isocortex and without significant numbers of neuritic senile plaques [23]. The clinical presentation is usually relatively mild, slowly progressive dementia that resembles AD and not FTD. Although astrocytic tau pathology is rare, argyrophilic grains and oligodendroglial coiled bodies are often present, suggesting that NFT-dementia and AGD may represent overlapping, age-related conditions.

Models and pathogenic mechanisms

Several basic features of human tauopathies have been recapitulated in model organisms. Experiments in *Caenorhabditis elegans* have supported the contributory role of tau in neurodegeneration, while those in *Drosophila* replicate tau hyperphosphorylation, fibril formation, and neurodegeneration. Although these experiments support the notion that the development of tau pathology is linked to clinical symptoms, they also raise the possibility that tau pathology may represent a cytoprotective mechanism aimed at sequestering abnormal tau [7, 24].

Transgenic mice show a variety of phenotypes and pathologic changes that vary with the specific mutations and gene promoters employed. These models include: (1) expression of human wild-type tau isoforms, (2) expression of human mutant tau isoforms, and (3) double and triple transgenic mouse models [24]. The associated pathology includes neuronal tangles, pre-tangles, and glial inclusions. Recent experimental studies that injected extracts from human post-mortem brain with various tauopathies,

into the brains of mice transgenic for wild-type human tau, recapitulated many of the hallmark pathologic lesions of the human conditions [25]. Moreover, these experiments demonstrated that once tau inclusions have formed in the brain, they may become self-propagating and spread in a prion-like manner. Taken together, these experimental approaches suggest that tau-mediated neurodegeneration may result from a toxic gain of function of the abnormal tau aggregates, deleterious effects due to the loss of normal tau function, or some combination of both [26].

FTLD-TDP

In 2006, TDP-43 was identified as the pathologic protein accumulating in the vast majority of cases classified as FTLD with ubiquitin-positive inclusions (FTLD-U) and in sporadic amyotrophic lateral sclerosis (ALS) [27]. Accordingly, this pathologic subgroup is now referred to as FTLD-TDP [3]. FTLD-TDP includes sporadic cases as well as familial forms of FTLD with an autosomal dominant pattern of inheritance and clinical symptoms of the FTD spectrum with or without additional features of ALS (Table 13.1). In most series, FTLD-TDP represents the most common pathology underlying FTD (Figure 13.1).

Normal TDP-43 expression and function

TDP-43 is a 414-amino acid protein encoded by the *TARDBP* gene on chromosome 1, consisting of two RNA recognition motifs, a glycine-rich C-terminal region, and a nuclear localization and nuclear export signal that allows TDP-43 to continuously shuttle between the nucleus and the cytoplasm (Figure 13.4). It is a highly conserved, ubiquitously expressed protein predominantly localized to the nucleus, and expression levels are

very tightly regulated by an autoregulatory mechanism. TDP-43 is involved in multiple steps of RNA processing including transcription, splicing, transport, and stabilization [28]. However, the precise functions of TDP-43, particularly in the central nervous system (CNS), are not fully elucidated.



Figure 13.4 Schematic representation of the TDP-43 protein. GRR, glycine-rich region; RRM, RNA recognition motif; NLS, nuclear localization signal; NES, nuclear export sequence.

TDP-43 in disease

The hallmark lesions of FTLD-TDP are neuronal cytoplasmic inclusions (NCI) and dystrophic neurites (DN) that are immunoreactive for TDP-43, as well as ubiquitin and p62, but negative for other neurodegenerative disease-related proteins, such as tau, α -synuclein, β -amyloid, and fused in sarcoma (FUS) [27]. NCI and DN are characteristically abundant in the frontotemporal neocortex and the dentate granule cells of the hippocampus (Figure 13.5A–G); however, notable differences exist in the morphology and laminar distribution patterns among FTLD-TDP cases, allowing the delineation of four subtypes (see below) (Table 13.2). In a subset of cases, particularly those with a positive family history, neuronal intranuclear inclusions (NII) are also present (Figure 13.5E). Most cases also show TDP-43 pathology in many subcortical regions, including the amygdala, striatum (Figure 13.5H), thalamus, substantia nigra, midbrain tectum and tegmentum, inferior olives, brainstem motor nuclei, and ventral gray matter of the spinal cord (Figure 13.5I). In addition, TDP-43 immunohistochemistry demonstrates previously unrecognized ubiquitin-negative pathology, including diffuse neuronal cytoplasmic staining (“pre-

inclusions”) ([Figure 13.5J](#)), delicate neurites in the CA1 region in a subset of FTLD-TDP ([Figure 13.5K](#)), and glial cytoplasmic inclusions (GCI) in cells of presumed oligodendroglial lineage ([Figure 13.5L](#)), that are most abundant in frontotemporal white matter, brainstem, and spinal cord [[29](#)].

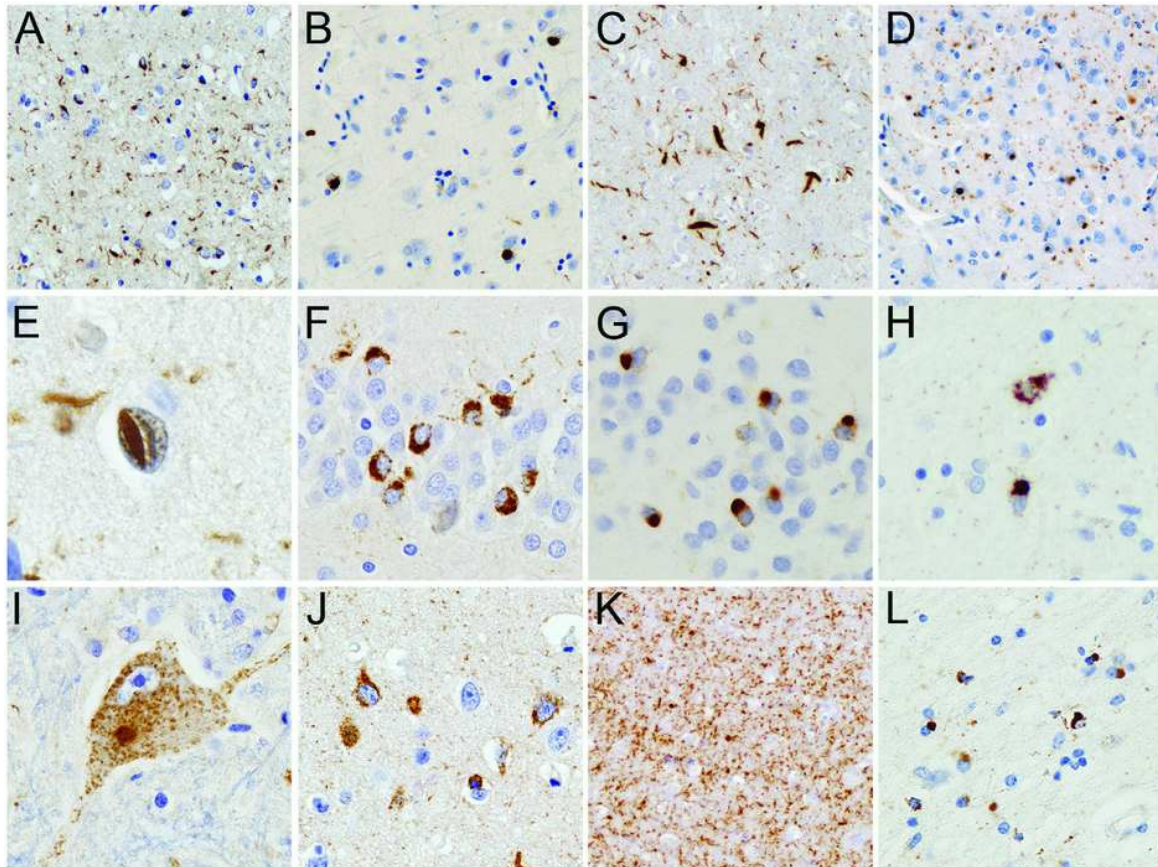


Figure 13.5 TDP-43-immunoreactive neuropathologic changes in FTLD-TDP. FTLD-TDP is characterized by neuronal cytoplasmic inclusions (NCI), neuronal intranuclear inclusions (NII), and dystrophic neurites (DN) in the frontotemporal neocortex (**A–E**) and dentate granule cell layer of the hippocampus (**F** and **G**) that are immunoreactive for TDP-43. Cases can be subclassified into FTLD-TDP type A in which both NCI and DN are numerous in layer II neocortex (**A**), FTLD-TDP type B with a predominance of NCI (**B**), FTLD-TDP type C with a predominance of elongated DN (**C**), and FTLD-TDP type D characterized by numerous DN and lentiform NII (**D** and **E**). Lesser numbers of NII are usually present in FTLD TDP type A cases and are a consistent finding of cases with progranulin gene mutations. NCI in

the dentate granule cells of the hippocampus may be granular (**F**) or compact (**G**). TDP-43 pathology may be found in many subcortical regions such as the striatum (**H**) and may be present in lower motor neurons, even in the absence of clinical motor neuron disease (**I**). Neurons with diffuse granular cytoplasmic reactivity for TDP-43 (pre-inclusions) are most common in cases with type B pathology and a consistent feature in FTD cases with motor neuron disease and those with *C9orf72* mutations (**J**). Numerous delicate DN in the CA1 region of the hippocampus may be associated with severe neuronal loss (hippocampal sclerosis) (**K**). TDP-43-immunoreactive glial cytoplasmic inclusions are present in cells with oligodendroglial morphology (**L**). TDP-43 immunohistochemistry.

Table 13.2 Neuropathologic subtypes of FTLD-TDP

Neocortical pathology ^{4}	Pathologic subtype			
	Type A	Type B	Type C	Type D
NCI	+++ Compact; layer II	++ Compact, granular, and pre-inclusions; all laminae	+	+
DN	+++ Short; layer II	+	+++ Long	+++ Short
NII	-/++	Usually absent	Usually absent	+++
NCI in dentate granule cells of hippocampus	+/ Granular	+++ Compact and granular	+/ Compact	-
Subcortical pathology	++/ NCI, DN; basal ganglia,	+/ NCI; brainstem, spinal cord	++/ NCI, DN;	+ NCI, DN,

thalamus, brainstem	basal ganglia	NII; basal ganglia
------------------------	------------------	--------------------------

^a Subtypes are defined by pattern of neocortical pathology.

DN = dystrophic neuritis, NCI = neuronal cytoplasmic inclusions, NII = neuronal intranuclear inclusions.

Semiquantitative grading: – = absent, + = few, ++ = moderate, +++, numerous.

FTLD-TDP is associated with several pathologic changes of TDP-43. The formation of TDP-43-positive inclusion bodies (either cytoplasmic or nuclear) is consistently associated with a dramatic reduction of the normally diffuse nuclear staining ([Figure 13.6A](#)) [27]. By immunoblot analysis, a distinct biochemical pattern of TDP-43 is seen in insoluble protein fractions isolated from post-mortem CNS tissue with the presence of FTLD-TDP specific bands at approximately 25 kDa and 45 kDa and a high molecular smear, in addition to the normal 43 kDa band ([Figure 13.6B](#)). The pathologic forms of TDP-43 show evidence of abnormal processing with hyperphosphorylation, ubiquitination, and N-terminal truncation [27]. Antibodies raised against phosphorylated epitopes of TDP-43 have further facilitated the detection of pathologic TDP-43 species, since they label only abnormal TDP-43 enriched in inclusions, but not the physiologic TDP-43 ([Figure 13.6B–C](#)) [30]. Notable differences are also present in the composition of inclusions with respect to the ratio of full-length TDP-43 versus N-terminally truncated TDP-43 species; while cortical inclusions are selectively enriched for hyperphosphorylated C-terminal TDP-43 fragments, spinal cord inclusions contain more full-length TDP-43 [30, 31].

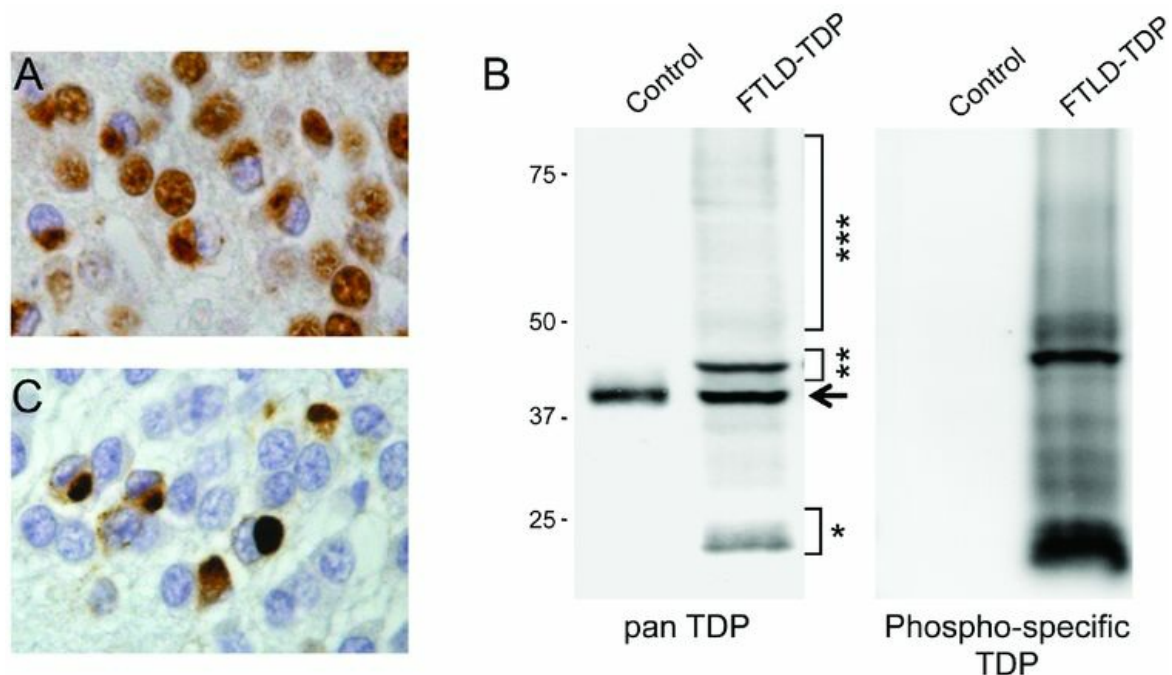


Figure 13.6 TDP-43 in FTLD-TDP. (A) Cytoplasmic accumulation of TDP-43 is associated with a dramatic decrease of the normal nuclear staining in inclusion-bearing cells, demonstrated with immunohistochemistry using a phosphorylation independent TDP-43 antibody. (B) Immunoblot analysis of urea fractions isolated from brain tissue show the highly characteristic biochemical signature of TDP-43 in FTLD-TDP, with pathologic bands of approximately 25 kDa (*) and 45 kDa (**), and a high-molecular-weight smear (***) that are not detected in controls. The arrow indicates the wild-type 43 kDa TDP-43 band present in controls and in FTLD-TDP patients. With a phosphorylation-specific TDP-43 antibody against phosphorylated serine residues 409 and 410, only pathologic TDP-43 species are detected on immunoblot (B) and in tissue sections (C).

Pathologic subtypes of FTLD-TDP

Prior to the identification of TDP-43 as pathologic protein in FTLD-U, it was noted in two independent studies that FTLD-U cases show a heterogeneous picture with respect to the morphology and laminar distribution of ubiquitin-positive inclusions in the frontotemporal neocortex and three distinct subtypes were delineated ([Table 13.2](#)) [32, 33].

Following the identification of TDP-43, and the confirmation that the vast majority of FTLD-U cases have TDP-43 pathology, the same criteria as described in the original ubiquitin immunohistochemistry-based studies were commonly used to subclassify FTLD-TDP cases [34]. Subsequently, a fourth subtype was added, corresponding to the unique pattern of ubiquitin and TDP-43 pathology in *VCP* mutation carriers [35]. While the findings in both initial typing studies were very similar, different numbering systems were used [32, 33]. To avoid confusion, a harmonized classification scheme was recently introduced, in which the previous numerical subtypes were replaced with subtypes A to D (Table 13.2) [36]. The relevance of the four distinct FTLD-TDP subtypes is supported by relatively specific correlations between the various patterns of pathology, the clinical phenotypes, and the known genetic causes in inherited forms of FTLD-TDP (Table 13.1).

FTLD-TDP type A

Type A cases are characterized by abundant short neuritic profiles and compact oval or crescentic NCI, predominantly in the superficial cortical layers (Table 13.2) (Figure 13.5A). Especially in cases with a positive family history, lentiform NII may be present in affected cortical regions (Figure 13.5E). NCI in the dentate granule cells of the hippocampus are variable in number and often show a granular composition (Figure 13.5F). Few to moderate numbers of GCI are usually present in the cerebral white matter. Frequently affected subcortical regions with TDP-43 pathology are the striatum, thalamus, and midbrain including the substantia nigra.

FTLD-TDP type B

Type B cases show moderate numbers of compact or granular NCI in both superficial and deep cortical layers with relatively few DN and NII (Table

[13.2](#); [Figure 13.5B](#)). TDP-43 immunohistochemistry often reveals numerous “pre-inclusions” in cortical and subcortical areas ([Figure 13.5J](#)). Characteristically and almost exclusive for type B is the presence of NCI in lower motor neurons, even in the absence of clinical features of ALS ([Figure 13.5I](#)). Usually, significant numbers of GCI are present in the cerebral white matter, medulla, and spinal cord.

FTLD-TDP type C

Type C cases have an abundance of long neuritic profiles, predominantly in the superficial cortical laminae, with few or no NCI ([Table 13.2](#); [Figure 13.5C](#)). Variable numbers of NCI are present in the hippocampus, usually with a compact, round morphology ([Figure 13.5G](#)). NII and GCI are uncommon.

FTLD-TDP type D

The characteristic feature of FTLD-TDP type D pathology is an abundance of lentiform NII and short DN with only rare NCI in neocortical regions ([Table 13.2](#); [Figure 13.5D–E](#)) and the absence of NCI in the hippocampal dentate granule cells.

Familial FTLD-TDP

FTLD-TDP due to GRN mutations

In 2006, mutations in the gene encoding progranulin (*GRN*) were identified in cases of autosomal dominant FTD linked to chromosome 17 that were not due to *MAPT* mutations [[37](#), [38](#)]. *GRN* mutations are at least as common in familial FTD as *MAPT* mutations, accounting for 5–20% of familial FTD and 25–50% of familial FTLD-TDP cases [[1](#)]. The clinical presentation is

most often bvFTD or PNFA. Extrapyrarnidal features (akinetie rigid syndrome or CBS) are common but ALS does not occur. Progranulin is a multifunctional secreted growth factor and all pathogenic mutations produce null alleles resulting in a reduction of functional progranulin (haploinsufficiency) [37, 38]. Consistent with this mechanism is the absence of progranulin in the ubiquitin-positive inclusions [37]. Instead, the ubiquitin-positive inclusions in FTLD with *GRN* mutations are positive for TDP-43 and show a highly consistent pattern of FTLD-TDP type A pathology (Figure 13.5A) [27, 34, 39]. In addition to abundant small NCI and DN in the superficial neocortex, all cases show moderate numbers of lentiform NII (Figure 13.5E). Numerous NCI, DN, and NII are usually seen in the striatum and are more variable in other subcortical regions. In the hippocampus, moderate numbers of TDP-43-positive NCI with a granular appearance are present in the dentate granule cells, and there is often significant loss of pyramidal neurons from the CA1 sector and the subiculum associated with numerous delicate DN (Figure 13.5K).

FTLD-TDP due to C9orf72 repeat expansion mutation

In 2011, abnormal expansion of a hexanucleotide (GGGGCC) repeat in a non-coding region of the *C9orf72* gene was identified as the genetic cause of chromosome 9p21-linked families in which affected members develop either FTD or ALS or both [40, 41]. Subsequently, this mutation was found to be the most common genetic abnormality in familial and sporadic forms of FTD and ALS and particularly frequent in patients with both conditions [1]. The most commonly associated FTD phenotype is bvFTD; however, a wide range of neurologic features are now recognized, including PNFA, memory deficits, extrapyramidal movement disorders, and psychosis. The neuropathology of *C9orf72* mutation carriers with a FTD or FTD-ALS

phenotype is a combination of FTLD-TDP and typical ALS. The pattern of neocortical TDP-43 is consistently described as FTLD-TDP type B ([Figure 13.5B](#) and [13.5J](#)); however, a subset of cases shows type B pathology in combination with FTLD-TDP type A. The presence of this dual pattern of FTLD-TDP has been strongly associated with advanced age and longer disease duration [[42](#)].

In addition to TDP-43 pathology, a unique and highly specific neuropathologic feature in *C9orf72* mutation cases is the presence of NCI and NII in the cerebellar granule cell layer, hippocampal pyramidal neurons, and other neuroanatomical sites that immunostain for markers of the ubiquitin proteasome system (UPS, such as ubiquitin, p62, and ubiquilin) but are negative for TDP-43 [[1](#)]. The major components of these inclusions have been characterized as dipeptide repeat (DPR) proteins that result from the unconventional translation of the expanded GGGGCC repeats in both sense and antisense direction and in all reading frames [[43](#), [44](#)]. DPR pathology is widespread, involving both degenerated and unaffected neocortical and subcortical regions as well as the cerebellum and hippocampus ([Figure 13.7](#)); however, it is extremely rare in the lower brainstem and spinal cord. Given the poor correlation of DPR pathology with neurodegeneration and clinical phenotypes, the pathologic significance of DPR pathology remains uncertain [[45](#)].

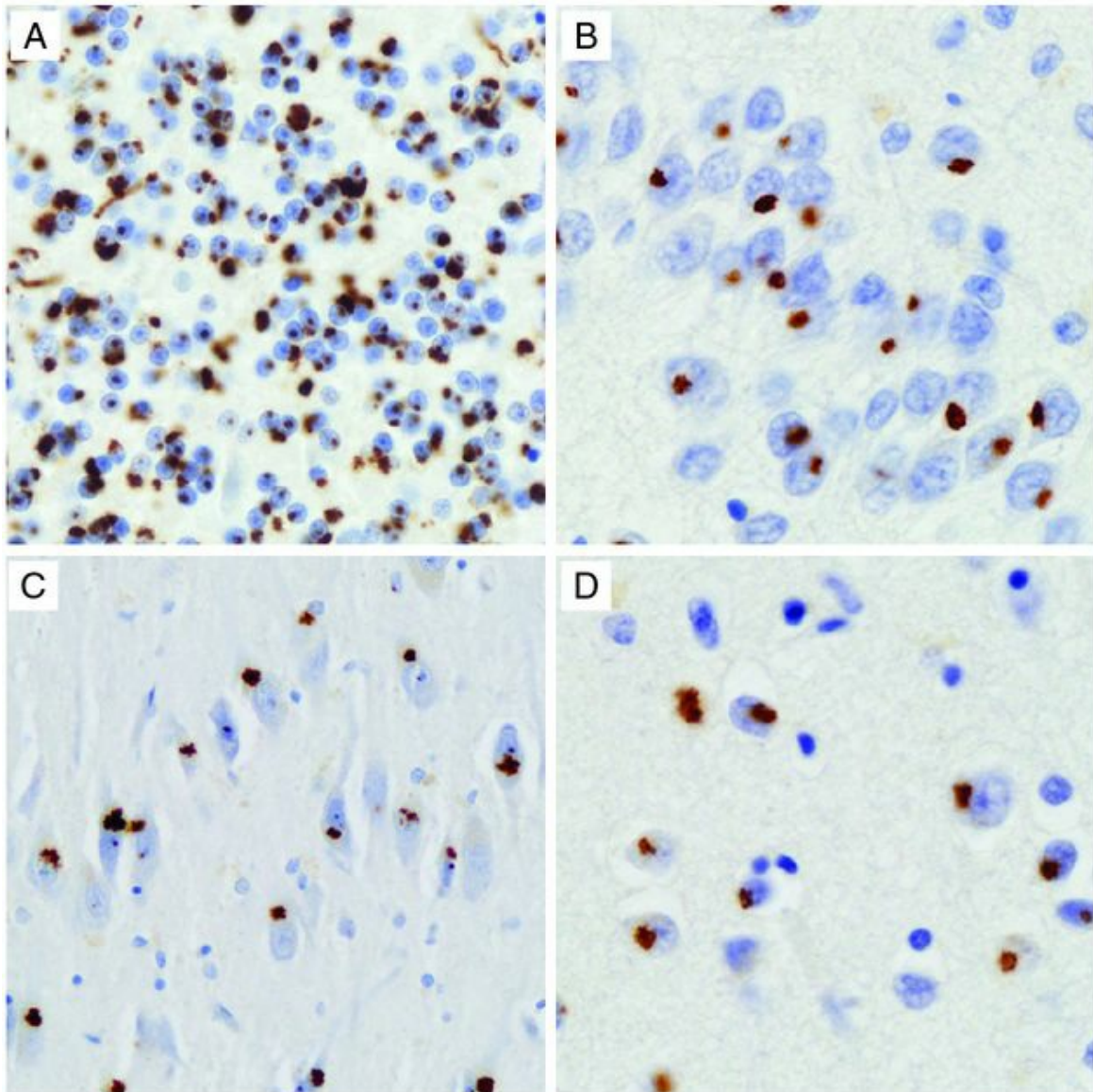


Figure 13.7 TDP-43-negative, dipeptide repeat protein pathology in FTLD-TDP with *C9orf72* mutation. A unique and consistent feature of cases with the *C9orf72* mutation is the presence of TDP-43-negative inclusions that are immunoreactive for dipeptide-repeat (DPR) proteins, generated by an unconventional translation of the abnormally expanded GGGGCC repeat. DPR-immunoreactive neuronal cytoplasmic inclusions and neuronal intranuclear inclusions are abundant in the cerebellar cortex (A), the dentate granule cells (B), the CA3/4 region of the hippocampus (C), and the neocortex (D). Immunohistochemistry with antibody against poly-GA DPR.

FTLD-TDP due to VCP mutations

Mutations in *VCP* are the cause of a rare familial syndrome in which inclusion body myopathy, Paget's disease of the bone, and FTD (IBMPFD) show variable penetrance [46]. VCP is a member of the AAA-ATPase protein superfamily, and functions as a molecular chaperone in a plethora of distinct cellular activities with many of them directly or indirectly regulated by the UPS [46]. The neuropathology in *VCP* mutation cases with FTD shows a unique and highly specific distribution of ubiquitin- and TDP-43-positive pathology designated as FTLD-TDP type D that is characterized by numerous NII and DN throughout all neocortical regions, with very few NCI (Figure 13.5D) [35]. The basal ganglia are usually mildly affected and a highly characteristic finding is the absence of TDP-43 pathology in the hippocampus.

FTLD-TDP due to TARDBP mutations

Mutations in the *TARDBP* gene encoding TDP-43 are usually associated with a clinical phenotype of pure ALS. They are a very rare genetic cause of FTD with one case reported with pure bvFTD and the N237S mutation [47], two unrelated patients reported with the G295S mutation and FTD-MND [48], and one patient with FTD, PSP, and chorea associated with the K263E mutation [49]. Neuropathologic information is only available for the single K263E case and is described as TDP-immunoreactive NCI, DN, and GCI, predominantly in subcortical nuclei and brainstem.

TDP-43 pathology in other neurodegenerative disease

A limited degree of TDP-43 pathology is found in ~25% of cases of AD, dementia with Lewy bodies (DLB), and many other neurodegenerative conditions [29]. It is most often restricted to the limbic structures of the mesial temporal lobe and shows only partial co-localization with the

disease-specific pathologic changes. The presence of this coexistent TDP pathology increases with age and is of uncertain pathogenic and clinical relevance.

Pathogenesis of FTLD-TDP

The molecular mechanisms underlying FTLD-TDP are complex and currently not well understood. The neuropathologic findings in sporadic and genetic forms of FTLD-TDP implicate both a loss-of-function and a gain-of-function mechanism of TDP-43-associated cell death as discussed in detail elsewhere [26, 29, 50, 51]. Briefly, the dramatic change in the subcellular distribution of TDP-43 from the nucleus to the cytoplasm in inclusion-bearing cells suggests a pathogenic mechanism associated with loss of pivotal physiologic TDP-43 functions in RNA processing. In support of this hypothesis is the early embryonic lethal phenotype of TDP-43 knockout mice and an ALS-like phenotype in mice with targeted depletion of TDP-43 in the spinal cord [52]. Given the plethora of > 6000 RNA binding partners of TDP-43 [51], a major challenge in the future will be to dissect and identify potential disease-relevant RNA targets. Alternatively or in combination, the generation and sequestration of abnormal TDP-43, such as C-terminal fragments and hyperphosphorylated species, might induce a toxic gain of function as suggested by several cell culture studies and in vivo models which demonstrate neurotoxicity upon overexpression of wild-type, mutant, or cytoplasmic TDP-43. However, it has to be noted that no TDP-43 model system so far has fully recapitulated the neuropathologic and biochemical features of human FTLD-TDP.

Another important but unresolved issue is the pathogenic significance of TDP-43 in the genetic forms of FTLD-TDP associated with *GRN*, *C9orf72*, and *VCP* mutations. The consistent presence of TDP-43 pathology,

with strong correlation between TDP-43 pathology and degeneration in key anatomical regions, argues for a central and crucial common downstream mechanism leading to TDP-43-mediated cell death in each of these genetic forms. However, the links between the distinct gene mutations and TDP-43 remain elusive. Moreover, the presence of non-TDP-43 pathology in *C9orf72* mutation cases raises the possibility of other pathways and proteins (e.g., DPR) being relevant in these cases.

FTLD-FET

Most cases of FTLD are characterized by pathologic changes that are immunoreactive for either tau or TDP-43. However, there remain 5–10% of FTLD cases, composed of a heterogeneous collection of uncommon disorders, for which the molecular basis remained largely unknown, until recently [53]. In 2009, mutations in the gene encoding the FUS protein (also known as translocated in liposarcoma, TLS) were discovered to cause a small proportion of familial ALS (ALS-FUS) [54, 55]. The recognized clinical, genetic, and pathologic overlap between ALS and FTD, and the high degree of functional homology between FUS and TDP-43, led to speculation that FUS might also be the pathologic protein in some cases of FTLD. In a series of studies, it was shown that antibodies against FUS labeled the characteristic cellular inclusions of most of the remaining tau/TDP-negative FTLD subtypes, including “atypical” FTLD-U (aFTLD-U) [53], neuronal intermediate filament inclusion disease (NIFID) [56], and basophilic inclusion body disease (BIBD) [57]. It was subsequently demonstrated that the pathologic inclusions in all these FTLD subtypes also contain the two other members of the FET family of proteins (Ewing's sarcoma [EWS] and TATA-binding protein-associated factor 15 [TAF15])

[58], as well as the protein responsible for transporting the FET proteins into the nucleus (transportin 1, Trn1) [59]. These findings indicated that aFTLD-U, BIBD, and NIFID share a common aberrant molecular pathway and are more closely related than previously recognized. As a result, these conditions have now been grouped together under the broad designation of FTLD-FET ([Table 13.1](#), [Figure 13.1](#)) [58].

Normal FET expression and function

The FET proteins were initially discovered as components of fusion oncogenes that cause specific types of human cancer [60, 61]. They are a family of ubiquitously expressed, homologous, DNA/RNA-binding proteins, involved in various aspects of DNA and RNA metabolism, including RNA transcription, processing, and transport; microRNA processing; and DNA repair. In most cell types, all of the FET proteins are predominantly localized to the nucleus, but they are able to continuously shuttle between the nucleus and cytoplasm. Protein-interaction studies have revealed that FET proteins are able to interact with each other, suggesting that they may form protein complexes. The normal physiologic role of FET proteins in the brain is not completely understood but some studies suggest that FUS may be involved in neuronal plasticity and the maintenance of dendritic integrity [62].

FET proteins in disease

In cases of FTLD-FET, immunohistochemistry with antibodies against the FET proteins demonstrates much more abundant pathology than other staining techniques [53, 56–58]. Although a proportion of the NCI and DN label for UPS proteins (e.g., ubiquitin and p62), more of these are FET-positive and there are some types of inclusions that are only appreciated

with FET immunohistochemistry, such as finely granular neuronal cytoplasmic “pre-inclusions” and glial cytoplasmic inclusions. All types of inclusions in all FTLD-FET subtypes label with antibodies against all three FET proteins ([Figure 13.8](#)) and double-labeling experiments show that the proteins often co-localize [[58](#)]. Immunohistochemistry using FUS and TAF15 antibodies show similar sensitivity, while staining for EWS is somewhat less sensitive and more variable; however, it is uncertain whether this reflects a true biochemical difference in the composition of the inclusions, or a limitation of the currently available EWS antibodies. Similar to TDP-43, cells with inclusions often show complete or partial reduction in the amount of normal diffuse nuclear staining, particularly for TAF15.

Although immunoblot analysis of FTLD-FET brain tissue demonstrates a relative shift of FET proteins to the insoluble fraction, initial studies failed to identify any abnormal molecular weight species [[53](#), [58](#)]. Moreover, the inclusions label with antibodies against various FET epitopes, suggesting that the pathologic species are the full-length proteins [[53](#)]. Recently, arginine hypomethylation was identified as a post-translational modification of FET proteins that appears to be disease specific and possibly related to the pathogenesis of FTLD-FET (see below) [[63](#)].

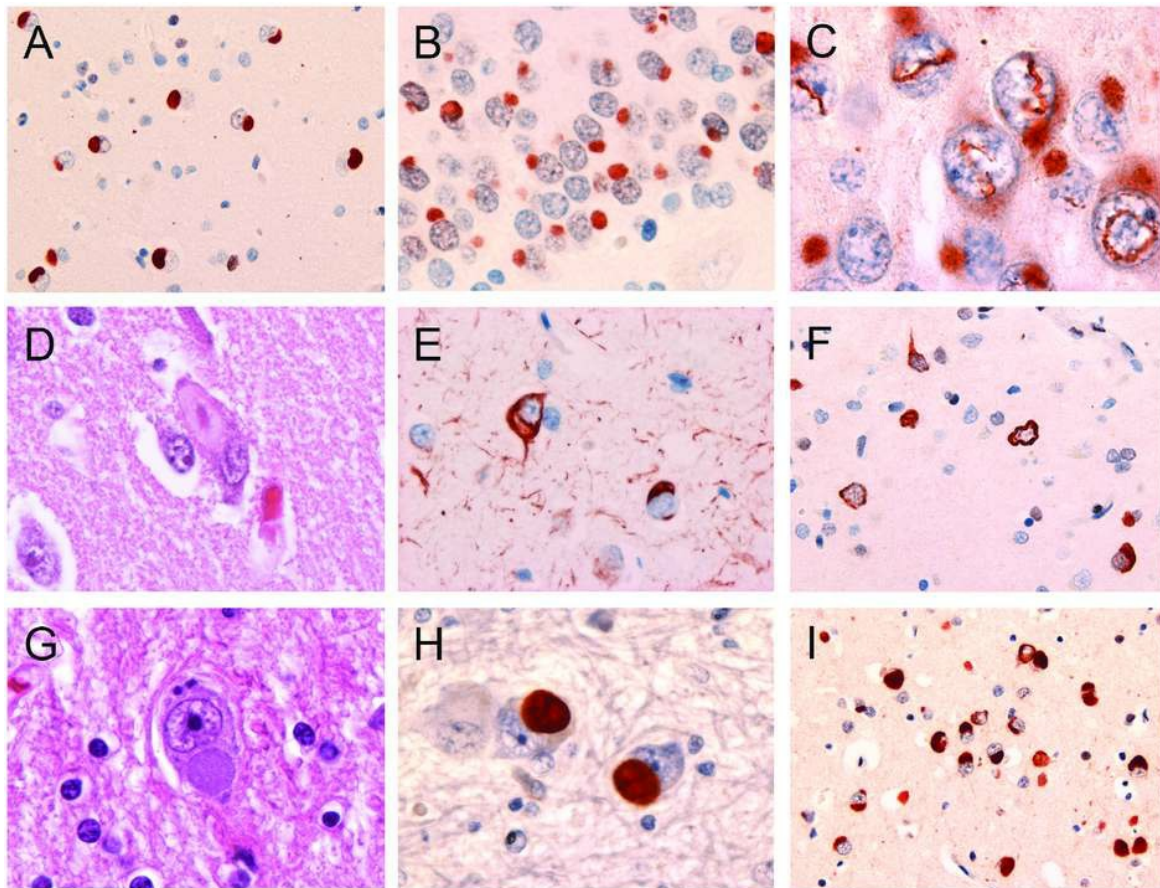


Figure 13.8 Neuropathologic features of FTLD-FET. (A–C) Atypical FTLD-U is characterized by compact oval neuronal cytoplasmic inclusions (NCI) (A and B) and filamentous neuronal intranuclear inclusions (C) in the neocortex (A) and hippocampus (B and C). (D–F) Neuronal intermediate filament disease (NIFID) has NCI of various morphologies, including hyaline conglomerates (D). Some are immunoreactive for class IV neuronal intermediate filaments (E); however, many more NCI are positive with FET immunohistochemistry (F). (G, H) Basophilic inclusion body disease is characterized by the presence of numerous round basophilic NCI (G) that are immunoreactive for all FET proteins (H). All types of FET-immunoreactive inclusions in all FTLD-FET subtypes also label for Trn1 (I). (A, C, F) FUS immunohistochemistry, (B) EWS immunohistochemistry, (H) TAF15 immunohistochemistry, (D, G) hematoxylin and eosin, (E) α -internexin immunohistochemistry, (I) Trn1 immunohistochemistry.

FTLD-FET subtypes

aFTLD-U, NIFID, and BIBD may be distinguished from one another pathologically by their characteristic types of NCI; frequent basophilic inclusions (BI) in BIBD [57], NCI-immunoreactive for neuronal intermediate filaments (IF) in NIFID [64], and NCI that are only detected by immunohistochemistry in aFTLD-U [65]. Although there is significant pathologic overlap, each FTLD-FET subtype shows relative differences that distinguished them from the others [66].

Atypical FTLD-U

Although initial studies suggested that TDP-43 was the ubiquitinated pathologic protein in all cases of FTLD-U [34], it was subsequently found that 10–20% of FTLD-U do not show evidence of abnormal TDP-43 [65]. The consistent and highly unusual clinical and pathologic features of these cases suggested that they represent a newly recognized, discrete entity and the term “atypical” FTLD-U (aFTLD-U) was introduced [65]. The clinical phenotype is sporadic, early-onset FTD with severe, rapidly progressive psychobehavioral changes in the absence of aphasia or significant motor features. In addition to frontotemporal atrophy, severe degeneration of the anterior striatum and hippocampal sclerosis are common. TDP-43-negative, ubiquitin/p62-positive NCI are most abundant in the frontal and temporal neocortices and hippocampus (Figure 13.8A–B). However, the most intriguing pathologic feature is the presence of NII in the dentate granule cells and cortical pyramidal neurons with a unique morphology, appearing as elongated straight or curved bars or thick twisted filaments (Figure 13.8C).

In cases of aFTLD-U, FET-immunoreactive pathology is most abundant in the cerebral neocortex, hippocampal dentate, and striatum [53, 66]. The predominant NCI morphology is small, compact, round or oval inclusions,

approximately the size of the nucleus ([Figure 13.8A–B](#)). Filamentous NII are consistently present in the hippocampus and common in the neocortex ([Figure 13.8C](#)). Compared with NIFID and BIBD, cases of aFTLD-U have less pathology in subcortical regions and more uniform inclusion morphology [[66](#)].

Neuronal intermediate filament inclusion disease

NIFID is an uncommon neurologic disorder with pathology characterized by neuronal inclusions that are immunoreactive for all of the class IV neuronal IF (light, medium, and heavy weight NF subunits and α -internexin). The typical clinical presentation is early-onset sporadic FTD, associated with a pyramidal and/or extrapyramidal movement disorder [[64](#)]. Additional clinical manifestations that have been reported include falls, dystonia, myoclonus, ophthalmoplegia, memory deficits, seizures, eating disorders, and psychiatric symptoms. Childhood onset and a possible family history have rarely been reported [[67](#)]. The neuropathologic findings in NIFID are heterogeneous [[64](#)]. Chronic degenerative changes may affect a variety of cortical and subcortical regions, with the frontal and temporal lobes and caudate nucleus most consistently and severely involved. Several different types of NCI and NII have been described that vary in morphology, histochemical staining, immunoreactivity, ultrastructure, and anatomical distribution ([Figure 13.8D](#)). By definition, these inclusions show no immunoreactivity for tau, α -synuclein, or TDP-43 but at least some are immunoreactive for neuronal IF. Antibodies against phosphorylated and phosphorylation-independent epitopes of all three NF subunits label some of the inclusions; however, α -internexin immunohistochemistry tends to be more sensitive ([Figure 13.8E](#)). Cases of NIFID have abundant and widespread FET-immunoreactive pathology with striking variation in the

inclusion morphology ([Figure 13.8F](#)) [[56](#), [66](#)]. In addition to cerebral cortex and hippocampus, all cases show involvement of basal ganglia, thalamus, cerebellar dentate, and numerous brainstem nuclei. NCI are also common in spinal cord lower motor neurons, even in cases without clinical ALS. NCI morphologies include round, crescentic, annular, tangle-like, granular, and complex non-compact collections of granules and filaments. Filamentous NII, similar to those of aFTLD-U, are found primarily in the hippocampus.

Basophilic inclusion body disease

BIBD is a term that has been used for a small number of clinically and pathologically heterogeneous cases, in which the common finding is NCI that are basophilic (stain with basic dyes) and appear blue-gray with hematoxylin and eosin stain ([Figure 13.8G](#)). The clinical phenotypes include sporadic ALS, familial ALS, ALS with dementia, and pure FTD [[57](#)]. Although cases of BIBD with clinical FTD show chronic degeneration of the frontotemporal neocortex, basophilic inclusions tend to be most numerous in subcortical regions, such as the basal ganglia and brainstem tegmentum. The inclusions are round, oval, or crescentic, weakly argyrophilic, and can be detected with histochemical stains for RNA.

In addition to the characteristic basophilic inclusions ([Figure 13.8H](#)), FET immunohistochemistry in cases of BIBD demonstrates a spectrum of NCI morphologies involving many cortical and subcortical regions, similar to NIFID [[57](#), [66](#)]. The severity of pathology in the hippocampus and striatum is somewhat more variable in BIBD than NIFID; however, the feature that most clearly discriminates BIBD on FET immunohistochemistry is the absence of NII [[66](#)].

FET proteins in other neurodegenerative diseases

In most other neurodegenerative conditions that have been studied, immunohistochemistry for FET proteins shows the normal nuclear staining pattern and fails to label the disease-specific inclusions. Exceptions are the characteristic NII of some repeat expansion disorders, such as Huntington's disease and spinocerebellar ataxia, which, in addition to the disease-specific mutant protein, also label for FUS and EWS but not TAF15, and intranuclear inclusion body disease in which the pathognomonic NII label for FUS but not the other FET proteins [58].

FTLD-FET pathogenesis

Mutations in the *FUS* gene are responsible for ~3% of familial ALS and ~1% of sporadic ALS [54, 55]. Most of pathogenic *FUS* mutations affect the C-terminus of the protein and disrupt the nuclear localization sequence, resulting in impaired Trn1-mediated nuclear import of FUS and increased concentrations of FUS in the cytoplasm [68]. This cellular mislocalization results in the recruitment of FUS into stress granules and the eventual formation of cellular inclusions that are immunoreactive for FUS, but not the other FET proteins [58, 68]. Abnormalities in the genes for EWS and TAF15 have also been reported in ALS [1]; however, the associated neuropathology is not currently known.

In contrast to ALS-FUS, cases of FTLD-FET are generally not associated with any mutation in *FUS* or the other FET protein genes [53, 58]. The fact that the inclusions in FTLD contain all FET proteins and Trn1 (Figure 13.8I), while immunohistochemistry for other Trn1 cargo proteins does not label the inclusions and demonstrates normal cellular localization, suggests that there is some abnormal post-translational modification that specifically affects all FET proteins and alters their interaction with Trn1 [59]. A recent study has suggested that arginine residues in the arginine–

glycine-rich region next to the nuclear localization signal of FET proteins are hypomethylated in FTLD, resulting in abnormally avid binding to Trn1 that could hamper dissociation of FET–Trn1 complexes and results in their accumulation in the cytoplasm [63]. The basis of this hypomethylation is not currently known, but it does not appear to be the result of alterations in the genes that encode the responsible protein *N*-arginine methyltransferases [69].

A number of experimental animal models of FUS proteinopathy have been developed, based on overexpression of mutant or wild-type human FUS, knockdown of wild-type FUS, or cellular mislocalization of FUS. Although some of these animals develop relevant phenotypes (motor, learning, and memory deficits) and pathology (neurodegeneration and cytoplasmic FUS aggregates), the results have not been consistent and the relative importance of loss of FUS function versus toxic gain of function remains unanswered [26].

FTLD-UPS

With the discovery of FET protein pathology in most of the remaining tau/TDP-negative forms of FTLD, it has become possible to assign the vast majority of FTLD cases to one of the three major molecular categories (FTLD-tau, FTLD-TDP, FTLD-FET). Cases characterized by cellular inclusions that are only identifiable with immunohistochemistry against markers of the UPS (ubiquitin, ubiquilins, p62) are now rare. One remaining example is familial FTD linked to chromosome 3 (FTD-3), due to mutations in *CHMP2B*. So far, five families have been identified with four different *CHMP2B* mutations (<http://www.molgen.ua.ac.be/FTDmutations>). *CHMP2B* belongs to the chromatin-modifying protein/charged

multivesicular body protein family and is a component of ESCRT-III (endosomal sorting complex required for transport III), a complex involved in the degradation of surface receptor proteins and the formation of endocytotic multivesicular bodies. The neuropathology of these cases is characterized by the presence of granular NCI, predominantly in the dentate granule cells of the hippocampus, that are immunoreactive for ubiquitin and p62, but negative for tau, TDP-43, and FUS [70, 71]. Whether this pathology indicates the accumulation of some disease-specific protein, or a more general defect in endosomal trafficking and lysosomal protein degradation remains to be clarified.

Other pathologic causes of FTD

There are a number of rare neurodegenerative conditions that typically present as FTD. These include hereditary diffuse leukoencephalopathy with spheroids, pigmented orthochromatic leukodystrophy, and Nasu–Hakola disease, which are each associated with mutations in genes related to macrophage/microglial activity (*CSFR1*, *TREM2*, and *DAP12*) and share similar neuropathologic features (myelin loss, axonal spheroids, and pigment accumulation in macrophages and glia) that preferentially affect the anterior cerebral white matter [72]. In addition, most of the common neurodegenerative causes of dementia can occasionally fulfill clinical diagnostic criteria for FTD. Although the frequency of these “frontal variants” and their overall contribution to FTD is difficult to determine, some studies have found more than 20% of clinical FTD to be associated with the pathology of AD, DLB, Creutzfeldt–Jakob, or vascular disease [73]. The frontal variant of AD is best recognized and may account for ~17% of all FTD [73]. Although some studies have demonstrated a

correlation between the regional (i.e., prefrontal) severity of the AD pathology and an FTD phenotype, this has not been consistent. One recent study has described additional glial tau pathology in cases of AD with clinical PPA, suggesting a pathologic overlap with FTLD-tau [74]. Finally, there remain very rare cases with clinical features of FTD and a frontotemporal pattern of chronic neurodegeneration in which even the use of immunohistochemistry fails to demonstrate the presence of any pathologic inclusions for which the designation FTLD-ni (for “no inclusions”) is appropriate.

Molecular correlates of FTD phenotypes

[Table 13.1](#) lists the molecular subtypes of FTLD pathology with the associated genetic defects and common clinical features. Each genetic cause is associated with a specific neuropathology. However, predicting the underlying molecular pathology or genetics, based on the pattern of inheritance and clinical features, is often imprecise [75]. SD is usually sporadic and associated with FTLD-TDP type C with fewer cases having the pathology of classical Pick's disease. Cases of sporadic PNFA are somewhat more likely to have FTLD-tau than FTLD-TDP, but bvFTD may be associated with any of the major pathologies. Early-onset bvFTD with severe psychobehavioral abnormality but minimal motor features or aphasia is characteristic of the aFTLD-U subtype of FTLD-FUS. When FTD is combined with ALS, the pathology is usually FTLD-TDP, whereas FTD with prominent parkinsonism is more often FTLD-tau (PSP or CBD). In families with autosomal dominant inheritance of bvFTD or PNFA without significant motor dysfunction, the underlying gene defect may be a mutation in *C9orf72*, *GRN*, or *MAPT*. When parkinsonism or PLS are also prominent

features, a *MAPT* mutation is more likely, whereas coexistence of classical ALS in a family strongly suggests a *C9orf72* mutation.

Conclusions

In the past decade there has been remarkable progress in our understanding of the molecular basis of FTD [1]. It appears that most of the common FTD-causing genes have now been discovered and the major pathologic proteins identified. Although many aspects of the specific pathogenic mechanisms still need to be resolved, we are now in a position to begin translating this newly acquired knowledge into improved FTD patient care. Advancing our knowledge of FTLD neuropathology and developing diagnostic tests that reflect these molecular pathologies in vivo will be crucial to the development of targeted therapies.

References

1. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol* 2012;**8**:423–34.
2. Mackenzie IR, Neumann M, Bigio EH, *et al.* Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. *Acta Neuropathol* 2009;**117**:15–18.
3. Mackenzie IR, Neumann M, Bigio EH, *et al.* Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol* 2010;**119**:1–4.
4. Weingarten MD, Lockwood AH, Hwo SY, *et al.* A protein factor essential for microtubule assembly. *Proc Natl Acad Sci USA* 1975;**72**:1858–62.

-
5. Goedert M, Spillantini MG, Jakes R, *et al.* Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron* 1989;**3**:519–26.
-
6. Spillantini MG, Goedert M. Tau pathology and neurodegeneration. *Lancet Neurol* 2013;**12**:609–22.
-
7. Lee G, Leurgers CJ. Tau and tauopathies. *Prog Mol Biol Transl Sci* 2012;**107**:263–93.
-
8. Iqbal K, Liu F, Gong CX, *et al.* Mechanisms of tau-induced neurodegeneration. *Acta Neuropathol* 2009;**118**:53–69.
-
9. Noble W, Hanger DP, Miller CC, *et al.* The importance of tau phosphorylation for neurodegenerative diseases. *Front Neurol* 2013;**4**:83.
-
10. van Swieten J, Spillantini MG. Hereditary frontotemporal dementia caused by tau gene mutations. *Brain Pathol* 2007;**17**:63–73.
-
11. Dickson DW, Rademakers R, Hutton ML. Progressive supranuclear palsy: pathology and genetics. *Brain Pathol* 2007;**17**:74–82.
-
12. Myers AJ, Pittman AM, Zhao AS, *et al.* The MAPT H1c risk haplotype is associated with increased expression of tau and especially of 4 repeat containing transcripts. *Neurobiol Dis* 2007;**25**:561–70.
-
13. Kovacs GG, Rozemuller AJ, van Swieten JC, *et al.* Neuropathology of the hippocampus in FTL D-tau with Pick bodies: a study of the BrainNet Europe Consortium. *Neuropathol Appl Neurobiol* 2013;**39**:166–78.
-
14. Dickson DW, Ahmed Z, Algom AA, *et al.* Neuropathology of variants of progressive supranuclear palsy. *Curr Opin Neurol* 2010;**23**:394–400.
-
15. Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. *J Neurol* 1999;**246** Suppl 2:116–15.

-
- 16.** Kouri N, Whitwell JL, Josephs KA, *et al.* Corticobasal degeneration: a pathologically distinct 4R tauopathy. *Nat Rev Neurol* 2011;**7**:263–72.
-
- 17.** Ahmed Z, Bigio EH, Budka H, *et al.* Globular glial tauopathies (GGT): consensus recommendations. *Acta Neuropathol* 2013;**126**:537–44.
-
- 18.** Ghetti B, Wszolek ZK, Boeve BF, *et al.* Frontotemporal dementia and parkinsonism linked to chromosome 17. In: Dickson DW, Weller RO, eds. *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*. Chichester, UK: Blackwell Publishing Ltd.; 2011; 110–34.
-
- 19.** Miki Y, Mori F, Hori E, *et al.* Hippocampal sclerosis with four-repeat tau-positive round inclusions in the dentate gyrus: a new type of four-repeat tauopathy. *Acta Neuropathol* 2009;**117**:713–18.
-
- 20.** Kovacs GG, Milenkovic I, Wohrer A, *et al.* Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol* 2013;**126**:365–84.
-
- 21.** Tolnay M, Probst A. Argyrophilic grain disease. *Handb Clin Neurol* 2008;**89**:553–63.
-
- 22.** Saito Y, Ruberu NN, Sawabe M, *et al.* Staging of argyrophilic grains: an age-associated tauopathy. *J Neuropathol Exp Neurol* 2004;**63**:911–18.
-
- 23.** Jellinger KA, Attems J. Neurofibrillary tangle-predominant dementia: comparison with classical Alzheimer disease. *Acta Neuropathol* 2007;**113**:107–17.
-
- 24.** Frank S, Clavaguera F, Tolnay M. Tauopathy models and human neuropathology: similarities and differences. *Acta Neuropathol* 2008;**115**:39–53.
-
- 25.** Clavaguera F, Akatsu H, Fraser G, *et al.* Brain homogenates from human

tauopathies induce tau inclusions in mouse brain. *Proc Natl Acad Sci USA* 2013;**110**:9535–40.

26. Halliday G, Bigio EH, Cairns NJ, *et al.* Mechanisms of disease in frontotemporal lobar degeneration: gain of function versus loss of function effects. *Acta Neuropathol* 2012;**124**:373–82.

27. Neumann M, Sampathu DM, Kwong LK, *et al.* Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;**314**:130–3.

28. Buratti E, Baralle FE. The multiple roles of TDP-43 in pre-mRNA processing and gene expression regulation. *RNA Biol* 2010;**7**:420–9.

29. Mackenzie IR, Rademakers R, Neumann M. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *Lancet Neurol* 2010;**9**:995–1007.

30. Neumann M, Kwong LK, Lee EB, *et al.* Phosphorylation of S409/410 of TDP-43 is a consistent feature in all sporadic and familial forms of TDP-43 proteinopathies. *Acta Neuropathol* 2009;**117**:137–49.

31. Igaz LM, Kwong LK, Xu Y, *et al.* Enrichment of C-terminal fragments in TAR DNA-binding protein-43 cytoplasmic inclusions in brain but not in spinal cord of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Am J Pathol* 2008;**173**:182–94.

32. Sampathu DM, Neumann M, Kwong LK, *et al.* Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies. *Am J Pathol* 2006;**169**:1343–52.

33. Mackenzie IR, Baborie A, Pickering-Brown S, *et al.* Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype. *Acta Neuropathol* 2006;**112**:539–49.

-
- 34.** Cairns NJ, Neumann M, Bigio EH, *et al.* TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. *Am J Pathol* 2007;**171**:227–40.
-
- 35.** Neumann M, Mackenzie IR, Cairns NJ, *et al.* TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. *J Neuropathol Exp Neurol* 2007;**66**:152–7.
-
- 36.** Mackenzie IR, Neumann M, Baborie A, *et al.* A harmonized classification system for FTL-D-TDP pathology. *Acta Neuropathol* 2011;**122**:111–13.
-
- 37.** Baker M, Mackenzie IR, Pickering-Brown SM, *et al.* Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* 2006;**442**:916–19.
-
- 38.** Cruts M, Gijselinck I, van der Zee J, *et al.* Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature* 2006;**442**:920–4.
-
- 39.** Mackenzie IR, Baker M, Pickering-Brown S, *et al.* The neuropathology of frontotemporal lobar degeneration caused by mutations in the progranulin gene. *Brain* 2006;**129**:3081–90.
-
- 40.** DeJesus-Hernandez M, Mackenzie IR, Boeve BF, *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;**72**:245–56.
-
- 41.** Renton AE, Majounie E, Waite A, *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;**72**:257–68.
-
- 42.** Hsiung GY, DeJesus-Hernandez M, Feldman HH, *et al.* Clinical and pathological features of familial frontotemporal dementia caused by *C9ORF72* mutation on chromosome 9p. *Brain* 2012;**135**:709–22.

-
- 43.** Mori K, Weng SM, Arzberger T, *et al.* The *C9orf72* GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTLD/ALS. *Science* 2013;**339**:1335–8.
-
- 44.** Ash PE, Bieniek KF, Gendron TF, *et al.* Unconventional translation of *C9ORF72* GGGGCC expansion generates insoluble polypeptides specific to c9FTD/ALS. *Neuron* 2013;**77**:639–46.
-
- 45.** Mackenzie IR, Arzberger T, Kremmer E, *et al.* Dipeptide repeat protein pathology in *C9ORF72* mutation cases: clinico-pathological correlations. *Acta Neuropathol* 2013;**126**:859–79.
-
- 46.** Kimonis VE, Fulchiero E, Vesa J, *et al.* VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: review of a unique disorder. *Biochim Biophys Acta* 2008;**1782**:744–8.
-
- 47.** Borroni B, Bonvicini C, Alberici A, *et al.* Mutation within *TARDBP* leads to frontotemporal dementia without motor neuron disease. *Hum Mutat* 2009;**30**:E974–83.
-
- 48.** Benajilba L, Le Ber I, Camuzat A, *et al.* *TARDBP* mutations in motoneuron disease with frontotemporal lobar degeneration. *Ann Neurol* 2009;**65**:470–3.
-
- 49.** Kovacs GG, Murrell JR, Horvath S, *et al.* *TARDBP* variation associated with frontotemporal dementia, supranuclear gaze palsy, and chorea. *Mov Disord* 2009;**24**:1843–7.
-
- 50.** Lee EB, Lee VM, Trojanowski JQ. Gains or losses: molecular mechanisms of TDP43-mediated neurodegeneration. *Nat Rev Neurosci* 2012;**13**:38–50.
-
- 51.** Da Cruz S, Cleveland DW. Understanding the role of TDP-43 and FUS/TLS in ALS and beyond. *Curr Opin Neurobiol* 2011;**21**:904–19.
-
- 52.** Wu LS, Cheng WC, Shen CK. Targeted depletion of TDP-43 expression in

the spinal cord motor neurons leads to the development of amyotrophic lateral sclerosis-like phenotypes in mice. *J Biol Chem* 2012;**287**:27335–44.

53. Neumann M, Rademakers R, Roeber S, *et al.* A new subtype of frontotemporal lobar degeneration with FUS pathology. *Brain* 2009;**132**:2922–31.

54. Kwiatkowski TJ, Jr., Bosco DA, Leclerc AL, *et al.* Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science* 2009;**323**:1205–8.

55. Vance C, Rogelj B, Hortobagyi T, *et al.* Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. *Science* 2009;**323**:1208–11.

56. Neumann M, Roeber S, Kretzschmar HA, *et al.* Abundant FUS-immunoreactive pathology in neuronal intermediate filament inclusion disease. *Acta Neuropathol* 2009;**118**:605–16.

57. Munoz DG, Neumann M, Kusaka H, *et al.* FUS pathology in basophilic inclusion body disease. *Acta Neuropathol* 2009;**118**:617–27.

58. Neumann M, Bentmann E, Dormann D, *et al.* FET proteins TAF15 and EWS are selective markers that distinguish FTLD with FUS pathology from amyotrophic lateral sclerosis with *FUS* mutations. *Brain* 2011;**134**:2595–609.

59. Neumann M, Valori CF, Ansorge O, *et al.* Transportin 1 accumulates specifically with FET proteins but no other transportin cargos in FTLD-FUS and is absent in FUS inclusions in ALS with *FUS* mutations. *Acta Neuropathol* 2012;**124**:705–16.

60. Tan AY, Manley JL. The TET family of proteins: functions and roles in disease. *J Mol Cell Biol* 2009;**1**:82–92.

61. Kovar H. Dr. Jekyll and Mr. Hyde: the two faces of the FUS/EWS/TAF15

protein family. *Sarcoma* 2011;**2011**:837474.

62. Fujii R, Takumi T. TLS facilitates transport of mRNA encoding an actin-stabilizing protein to dendritic spines. *J Cell Sci* 2005;**118**:5755–65.

63. Dormann D, Madl T, Valori CF, *et al.* Arginine methylation next to the PY-NLS modulates transportin binding and nuclear import of FUS. *EMBO J* 2012;**31**:4258–75.

64. Cairns NJ, Grossman M, Arnold SE, *et al.* Clinical and neuropathologic variation in neuronal intermediate filament inclusion disease. *Neurology* 2004;**63**:1376–84.

65. Mackenzie IR, Foti D, Woulfe J, *et al.* Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions. *Brain* 2008;**131**:1282–93.

66. Mackenzie IR, Munoz DG, Kusaka H, *et al.* Distinct pathological subtypes of FTL-D-FUS. *Acta Neuropathol* 2011;**121**:207–18.

67. Mackenzie IR, Feldman H. Neurofilament inclusion body disease with early onset frontotemporal dementia and primary lateral sclerosis. *Clin Neuropathol* 2004;**23**:183–93.

68. Dormann D, Rodde R, Edbauer D, *et al.* ALS-associated fused in sarcoma (FUS) mutations disrupt transportin-mediated nuclear import. *EMBO J* 2010;**29**:2841–57.

69. Ravenscroft TA, Baker MC, Rutherford NJ, *et al.* Mutations in protein N-arginine methyltransferases are not the cause of FTL-D-FUS. *Neurobiol Aging* 2013;**34**:2235.e11–13.

70. Holm IE, Englund E, Mackenzie IR, *et al.* A reassessment of the neuropathology of frontotemporal dementia linked to chromosome 3. *J Neuropathol Exp Neurol* 2007;**66**:884–91.

71. Holm IE, Isaacs AM, Mackenzie IR. Absence of FUS-immunoreactive pathology in frontotemporal dementia linked to chromosome 3 (FTD-3) caused by mutation in the *CHMP2B* gene. *Acta Neuropathol* 2009;**118**:719–20.

72. Wider C, Van Gerpen JA, DeArmond S, *et al.* Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD): a single entity? *Neurology* 2009;**72**:1953–9.

73. Forman MS, Farmer J, Johnson JK, *et al.* Frontotemporal dementia: clinicopathological correlations. *Ann Neurol* 2006;**59**:952–62.

74. Munoz DG, Woulfe J, Kertesz A. Argyrophilic thorny astrocyte clusters in association with Alzheimer's disease pathology in possible primary progressive aphasia. *Acta Neuropathol* 2007;**114**:347–57.

75. Josephs KA, Hodges JR, Snowden JS, *et al.* Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol* 2011;**122**:137–53.

Chapter 14

Genetics of frontotemporal dementia and related disorders



Marc Cruts and Christine Van Broeckhoven

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Recent molecular genetics breakthroughs in frontotemporal lobar degeneration (FTLD) and related disorders include the identification of novel rare mutations causing Mendelian forms of FTLD, including granulin loss-of-function mutations and pathologic *C9orf72* repeat, and the first common risk gene *TMEM106B*. The identification of the GGGGCC repeat expansion in *C9orf72* has revealed the molecular basis of the clinical and neuropathologic overlap between FTLD and amyotrophic lateral sclerosis. Together, the identification of these novel FTLD genes has been the basis of the currently emerging disease mechanisms associated with FTLD and related disorders. These novel insights will facilitate progress in the development of therapeutic strategies. Yet, our current understanding of the wide clinical variability associated with FTLD genes is still largely enigmatic. Continued efforts to identify additional Mendelian, risk, and

modifying genes promises accelerated progress into downstream translational research.

Introduction

With a positive family history of disease in 40–50% of frontotemporal lobar degeneration (FTLD) patients [1–6], FTLD has a strong genetic component. At least 10% to up to 50% of these families are associated with an inheritance pattern compatible with a highly penetrant Mendelian mutation. Family history is most prominent in behavioral variant FTD (bvFTD) (45%), especially when concomitant symptoms of motor neuron disease (MND) are present (60%), while semantic dementia (SD) appears to be the least hereditary FTLD subtype (< 20%). Molecular genetic studies have identified Mendelian mutations in five genes: granulin (*GRN*), chromosome 9 open reading frame 72 (*C9orf72*), and the genes encoding the microtubule-associated protein tau (*MAPT*), the valosin-containing protein (*VCP*), and the charged multivesicular body protein 2B (*CHMP2B*) (AD & FTLD Mutation Database) [7]. In addition, mutations in the genes encoding transactive response DNA-binding protein 43 (TDP-43) (*TARDBP*) and fused in sarcoma (*FUS*), which typically cause amyotrophic lateral sclerosis (ALS), in rare cases result in a clinical picture of FTLD [8], with or without observed signs of MND. The relative mutation frequencies of these genes vary substantially among different studies because of population-specific founder effects resulting in a regionally high occurrence of one or a limited number of specific mutations [7]. Nevertheless, in general terms, mutations in *C9orf72*, *GRN*, and *MAPT* are the most common and together explain at least 17% and up to 40% of familial FTLD [1]. As the mutant gene is at the basis of the pathobiologic processes underlying the

neuropathologic changes, a strong correlation is observed between the disease gene and type of neuropathology. In addition to harboring rare but highly penetrant Mendelian FTLN mutations, frequent genetic variations in *MAPT*, *GRN*, and *C9orf72* have been associated with disease risk. Further, a genome-wide association study (GWAS) in FTLN-TDP (FTLN with TDP-43 proteinopathy) identified *TMEM106B* as a novel risk gene [9]. In this chapter, we will discuss in detail the molecular genetics of the known causative and risk genes for FTLN, and describe clinical and neuropathologic correlations.

Mendelian FTLN genes

MAPT

The first genetic linkage studies in autosomal dominant FTLN families identified a locus at chromosome 17q21 in 13 families, in which a consensus clinical syndrome termed FTDP-17 was described which was referred to as autosomal dominant disinhibition, dementia, parkinsonism, and amyotrophy [10]. One of the genes located in the shared linked region was the gene encoding microtubule-associated protein tau (*MAPT*), the constituent of Alzheimer-like neurofibrillary tangles (NFTs) that were a neuropathologic hallmark of some but not all FTDP-17 families. Extensive mutation analyses identified *MAPT* mutations in patients of some of the linked families [11]. Today, 44 different *MAPT* mutations are reported in 138 FTLN families (Table 14.1) [7]. Based on their pathobiologic mode of action, two different types of *MAPT* mutations are described: the first type deregulates gene splicing, while the second type disturbs microtubule binding. *MAPT* is widely expressed in all tissues, with highest expression in the nervous system, where tau has multiple neuronal functions including

regulation of microtubule assembly and stability. As such, it plays a role in neuronal plasticity and kinesin-mediated anterograde axonal transport. In the normal brain, *MAPT* is transcribed into six different transcript variants resulting from alternative splicing of exons 2, 3, and 10 of, in total, 13 coding exons. Exons 10 to 13 encode 4 microtubule-binding domains, and depending on the spatiotemporally tightly regulated inclusion or exclusion of exon 10, tau isoforms containing three (3R tau) or four microtubule-binding domains (4R tau) are produced. The first group of *MAPT* mutations clusters in the exonic and intronic sequences near the intron 10 splice donor site and disrupts exon 10 splicing. These mutations result in a disturbed 4R/3R tau protein ratio [12], which in turn interferes with the subtle equilibrium of cytoskeletal assembly and disassembly affecting neuronal plasticity and axonal transport across the microtubules. Intronic mutations near the intron 9 splice acceptor may have a similar effect. The second group of mutations consists of missense mutations and in-frame single-codon deletions, clustered in the five most 3' exons 9 to 13, encoding the microtubule-binding domains. As a result, these mutations affect the binding kinetics of tau to microtubules and in vitro assays demonstrated disturbed microtubule assembly dynamics. In addition, these mutations may accelerate the formation of neurotoxic tau filaments constituting the NFTs. Missense mutations located in exon 10 may result in a combination of effects attributed to both *MAPT* mutation types [13].

Table 14.1 FTL genes and their mutation frequencies in FTLD

Gene symbol	Chromosomal location	Mutation frequency ^a	Number of mutations ^b	Number of independent observations ^b	Pro
<i>C9orf72</i>	9p21.2	10–30%	1	336	FTL type

<i>GRN</i>	17q21.32	10–25%	69	264	FTL type
<i>MAPT</i>	17q21.1	5–20%	44	138	FTL
<i>VCP</i>	9p13.3	<1%	17	49	FTL type
<i>CHMP2B</i>	3p11.2	<1%	4	5	FTL
<i>FUS</i>	16p11.2	<1%	23	54	FTL aFTL
<i>TARDBP</i>	1p36.22	<1%	34	95	FTL

^a Mutation frequencies are taken from larger studies reported in literature [13, 33, 80].

^b Numbers based on the AD & FTLD Mutation Database [7].

aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; FTLD, frontotemporal lobar degeneration; FUS, fused in sarcoma; TDP, transactive response DNA-binding protein; UPS, ubiquitin proteasome system.

Tau mutations are associated with neuronal intracytoplasmatic inclusions including spherical aggregations termed Pick bodies after the neurologist Arnold Pick, who first described these pathologic hallmarks in the granular neurons of the dentate gyrus and pyramidal neurons of the hippocampus and neocortical regions. These inclusions are primarily composed of pathological tau proteins. The term FTLD-tau is now used to identify this neuropathologic type of FTLD (see [Chapter 13](#)). FTLD-tau, usually but not always manifesting as bvFTD or progressive non-fluent aphasia (PNFA), is characterized by the earliest mean onset age of 48 ± 10 years, although the onset age range between 22 and 75 years [14] is wide

and overlapping with other FTLT types ([Figure 14.1](#)). In addition to FTLT-tau, *MAPT* mutations have been associated with other tauopathies, including progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and argyrophilic grain disease (AGD) [[15](#)].

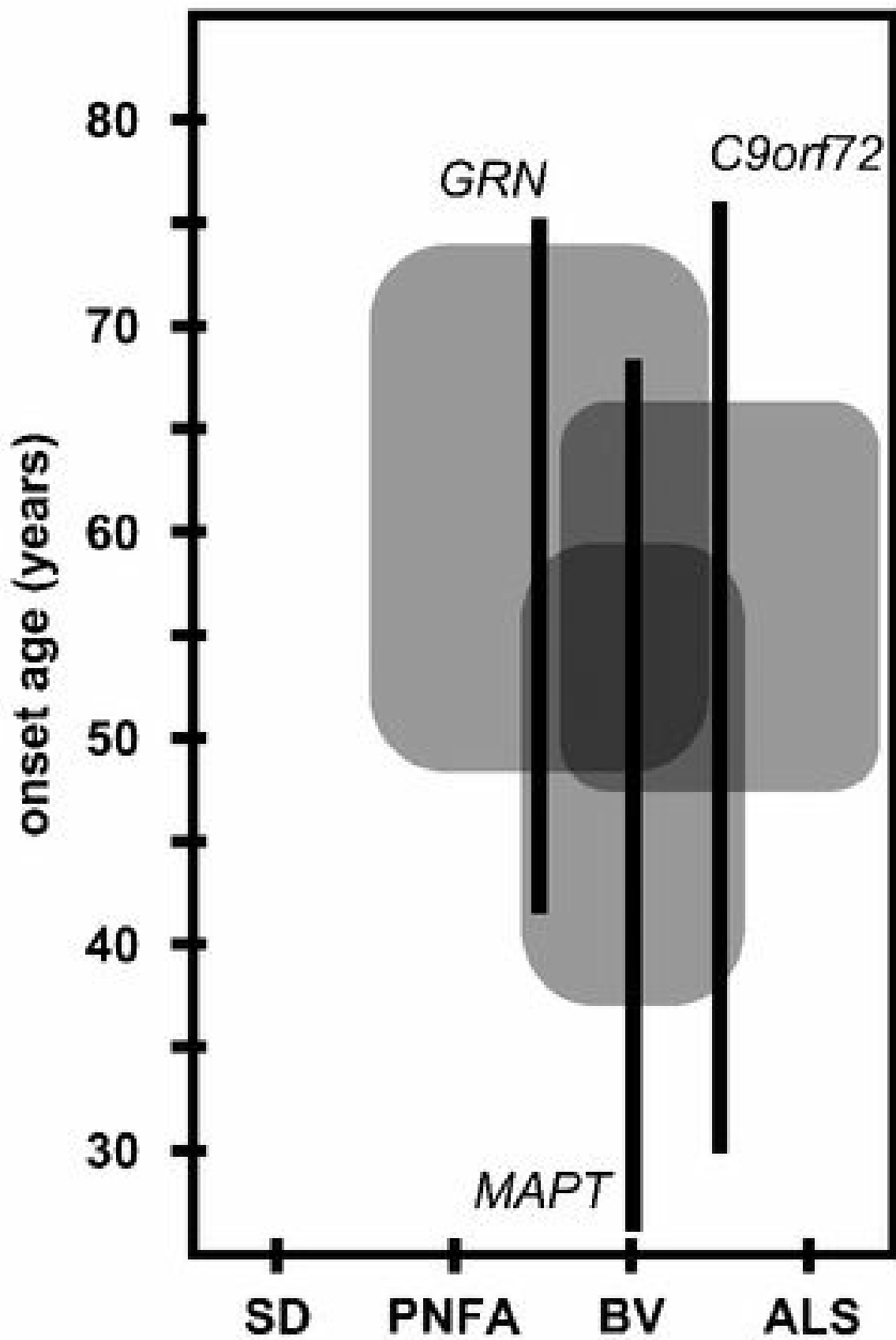


Figure 14.1 Clinical characteristics associated with the major FTL genes *GRN*, *C9orf72*, and *MAPT*. Shaded areas represent interquartile distribution

of onset age (y-axis) and FTLD subtype (x-axis). Vertical lines represent standard deviations of onset ages. Based on AD & FTLD Mutation Database [7].

GRN

Despite extensive mutation analyses, a *MAPT* mutation could not be identified in all FTLD families linked to chromosome 17q21. When it became apparent that in these FTLD families the ubiquitin-positive inclusions were tau-negative, a different genetic cause of disease was anticipated. Mutation analyses of other genes in the chromosome 17q21 region identified mutations in *GRN*, located 1.5 Mb centromeric of *MAPT* [16, 17]. To date, 69 different *GRN* mutations have been reported in 264 families (Table 14.1) [7]. *GRN* encodes progranulin, a ubiquitously expressed growth factor precursor which is processed into 7.5 granulin peptides [14]. Both full-length progranulin and the granulin peptides are implicated in a wide range of biologic processes such as inflammation and wound repair, as well as in pathologic conditions including tumorigenesis. Although the roles of progranulin and the processed granulin peptides in the central nervous system are not well established, in vitro and in vivo studies suggest a neurotrophic function involved in neuronal survival and neurite outgrowth [18]. *GRN* mutations linked with FTLD lead to the loss of one functional allele. Most mutations produce null alleles as a result of mRNA decay mediated by a nonsense mutation, or frameshift mutation introducing a premature termination codon. Other loss-of-function mechanisms including gene deletion, mutations interfering with protein sorting, and mutations disrupting protein structure were reported. As a result, these mutations cause FTLD through a haploinsufficiency mechanism [14].

The functional impact of *GRN* missense mutations and their association with disease is less straightforward: some compromise protein stability or

cellular sorting and may result in loss of function. Examples of such loss-of-function missense mutations are those disrupting the signal peptide or the cysteine disulfide bonds controlling the characteristic granulin peptide fold. Other missense mutations are more likely to partially compromise granulin function and behave as risk alleles [14]. *GRN* missense mutations have been suggested to be rare risk variations in Alzheimer's disease (AD) [19, 20], and ALS [21]. Using circulating granulin levels in cerebrospinal fluid, serum, or plasma as a protein biomarker may be an informative discriminator between benign and risk variations.

All *GRN*-associated FTLD patients develop a FTLD-TDP proteinopathy type A, characterized by numerous short dystrophic neurites (DN) and neuronal cytoplasmic TDP-43 inclusions (NCI) in the superficial cortical layers of the brain (see [Chapter 13](#)). Of the FTLD-TDP type A patients, *GRN* mutations explain about 40% [22]. Despite the fact that haploinsufficiency is the common disease mechanism in all patients carrying a *GRN* mutation, the associated clinical phenotype is variable, including bvFTD and PNFA [23]. Clinical diagnoses of related neurodegenerative diseases, including AD and parkinsonian disorders, have been associated with *GRN* mutations [23, 24]. A clinical review of 97 *GRN* mutation carriers noted a diagnosis of AD in 11% and parkinsonian symptoms and motor neuron symptoms were each observed in 5% of *GRN* mutation carriers [25]. A literature survey of 183 patients with *GRN*-associated FTLD demonstrated that the mean onset age was 61 ± 9 years, i.e., 13 years later than in *MAPT* mutation carriers ([Figure 14.1](#)) although, as in FTLD-tau, there is a wide distribution of onset ages, ranging from 35 to 87 years [7, 14]. Age-dependent penetrance was observed, with 50–60% of mutation carriers being affected by 60 years and 90–95% by age 70 years [26], resulting in an often unrecognized family history. Consequently up to 25% of

patients with a *GRN* mutation are diagnosed with sporadic FTLD [25]. In this group of patients, *GRN* mutations explain 3%.

C9orf72

Although signs of ALS occur in as much as 15% of FTLD patients, neither *MAPT* nor *GRN* mutations were associated with FTLD-ALS. In such families segregating FTLD and ALS, genome-wide linkage studies identified a disease locus at chromosome 9p13–p21 [27, 28]. Since the first identification of this locus, more than 15 autosomal dominant families with ALS and FTLD worldwide were genetically linked to the same chromosomal region, suggesting a major disease locus for FTLD-ALS. Meanwhile, genome-wide association studies in ALS patients of European origins demonstrated that the same chromosomal region harbored a genetic risk factor for ALS, FTLD, and ALS-FTLD. In a Finnish ALS study the susceptibility region was narrowed to a 232 kb genomic segment containing three protein-coding genes [29]. The genomic region shared between the FTLD linkage and ALS association studies and the extensive mutation analyses of all genes in that region resulted in the identification of a pathologically expanded GGGGCC hexanucleotide repeat in the regulatory region of *C9orf72* associated with FTLD and ALS [30–32]. In Western Europe and North America, the normal GGGGCC repeat size is smaller than 25 units, while in Asian populations the normal repeat size range does not exceed 15 units [33]. In contrast, the size of pathologically expanded repeat alleles is generally larger than 60 repeat units [33] and can extend to over 4000 repeat units.

Numerous studies worldwide confirmed that the GGGGCC repeat expansion in *C9orf72* is the most common cause of diseases in the FTLD-ALS continuum. Globally, frequencies are the highest in White populations

of Europe and North America, ranging from 3.5% to 18% in FTLN (Table 14.1), 7% to 28% in ALS, and 15% to more than 50% in FTLN-ALS [33]. In European populations, frequencies were markedly elevated in ALS patients of Finland, Sweden, and Denmark. In strong contrast, pathologic repeat expansions were rarely observed in Asian populations, with frequencies of 0.4–4.8% in ALS [34]. Based on these observations and the fact that the repeat expansions occur on the same haplotype, some studies suggested a common northern European founder [35]. In contrast, a detailed study rather supported multiple independent expansion events on the same haplotype, possibly harboring repeat-destabilizing elements [36]. Patients with a family history of disease showed 3 to 12 times higher frequencies compared with non-familial patients. Nevertheless, especially in ALS, where family history is observed in only 10% of patients, sporadic ALS patients carrying an expanded repeat outnumber familial ALS patients. In both, FTLN (AD & FTLN Mutation Database [7]) and ALS (ALS Online Genetics Database [37]), the frequency of *C9orf72* repeat expansions significantly exceeded that of any other individual mutation causing disease. The highest mutation frequencies were recorded in familial patients with combined FTLN and ALS symptoms.

C9orf72 encodes a ubiquitously expressed protein of unknown function. It is expressed as three major transcripts which are translated in two different protein isoforms. The expanded GGGGCC repeat is located in the non-coding, proximal regulatory region of *C9orf72* [33]. Pathologic repeat expansions result in near-complete loss of expression of the three major gene transcripts [30–32], suggesting that haploinsufficiency contributes to the disease mechanism. In addition, accumulation of transcripts harboring the expanded GGGGCC repeat in nuclear RNA foci was described [30, 38]. Detailed studies of such RNA foci in other repeat expansion diseases such as Huntington's disease and spinocerebellar ataxias

have demonstrated that they mediate a toxic gain of RNA function. In this mechanism, RNA species containing expanded repeats bind select RNA-binding proteins (RBPs), thereby disrupting their normal function. Interestingly, GGGGCC repeats were shown to bind heteronuclear RNA-binding protein A3 (hnRNPA3), which accumulates in neuronal cytoplasmic and intranuclear inclusions in the hippocampus [39]. Recently, the expanded repeat sequences were also demonstrated to be transcribed into abnormal sense and antisense RNA species. In addition to potentially contributing to the formation of RNA foci, they were actively translated into five different dipeptide repeats (DPRs), depending on the reading frame [40]. These DPRs were shown to be a component of the star-shaped intraneuronal aggregates/inclusions in the hippocampus, cerebellum, and neocortex, specific to *C9orf72* expansion carriers.

Neuropathologically, FTLN-*C9orf72* is generally associated with TDP-43 proteinopathy type B, characterized by NCI throughout the cortex, hippocampus, and in some patients also in motor neurons and spinal cord (see [Chapter 13](#)). Motor neurons and spinal cord involvement were associated with clinical signs of MND [38]. However, the number and distribution of TDP-43 inclusion pathology was variable and in some patients more consistent with a TDP-43 type A [41] or FTLN-ubiquitin proteasome system (UPS), lacking detectable TDP-43 neuropathology [32, 42]. Abundant star-shaped, p62-positive and TDP-43-negative NCI, and rare neuronal intranuclear inclusions (NII) were seen in the pyramidal cell layer of the hippocampus and cerebellar granular layer of most patients. These inclusions were shown to be highly specific for the *C9orf72* mutation carriers and contain DPRs translated from the expanded hexanucleotide repeats as well as RBPs, including hnRNAP3 [39, 40].

Patients with a *C9orf72* repeat expansion clinically present with widely variable symptoms of the FTLN-ALS spectrum including FTLN,

ALS, and FTLD-ALS [33]. Independent of concomitant ALS, FTLD is mostly of the behavioral type but patients with PNFA have been described. The mean onset age is 57 years [34, 43], which is intermediate to the mean onset ages in FTLD associated with *MAPT* and *GRN* (Figure 14.1). Also here, a high variability in onset age was noted, ranging between 30 and 76 years [34]. Typical of repeat expansion diseases, genetic anticipation has been suggested with a 7-year decreased onset age in the two succeeding generations [44]. However, inverse correlation of repeat expansion size and onset age needs to be demonstrated.

VCP

Linkage analysis and subsequent mutation analyses in autosomal dominant families with a multisystem proteinopathy characterized by inclusion body myopathy (IBM), Paget's disease of the bone (PDB), and FTLD (IBMPFD) identified mutations in *VCP* at chromosome 9p13 [45]. Today, 19 different mutations have been identified in 49 independent families (AD & FTLD Mutation Database [7]). *VCP* encodes a ubiquitously expressed member of a family of AAA-ATPases associated with many cellular functions through interactions with different adaptor proteins. All IBMPFD mutations affect amino acid residues located at the interface between the D1 ATPase and the CDC48-like N domain of the protein [46]. The best supported hypotheses of the disease mechanism of *VCP* mutations are disturbed ubiquitin-mediated proteasomal protein degradation [47] and autophagy, possibly acting in a concerted fashion [48].

FTLD patients with a *VCP* mutation are associated with TDP-43 proteinopathy type D, characterized by large numbers of NCI, NII, and DN in affected neocortical regions [5]. Some inclusions also stain for VCP protein p97 [49]. Symptoms of FTLD due to a *VCP* mutation usually present

in the mid-50s in 25–30% of IBMPFD patients [45]. Because the symptoms of the IBMPFD syndrome display incomplete penetrance, patients may present with classical FTLD. Nevertheless, in classical FTLD, *VCP* mutations are rare and represent less than 1% of familial FTLD (Table 14.1). The most frequently reported FTLD subtypes associated with a *VCP* mutation are bvFTD and SD [50]. Interestingly, motor neuron involvement was reported in IBMPFD and *VCP* mutations were reported in 1–2% of ALS patients [51].

CHMP2B

In a Danish FTLD family with particular neuropathologic features characterized by vacuolar abnormalities in cortical neurons and negative for tau, TDP-43, and FUS antibodies, linkage analyses identified a mutation in *CHMP2B* at chromosome 3p11.2 [52]. Subsequent mutation analyses identified four mutations in five families (Table 14.1) (AD & FTLD Mutation Database [7]). The mutation of the Danish family and a more recently identified nonsense mutation in exon 5 of 6 were both shown to result in C-terminal protein truncation, by aberrant exon splicing [52] and introducing a premature termination codon [53], respectively. Nevertheless, missense mutations were also reported. *CHMP2B* encodes a component of the heteromeric ESCRT-III (endosomal sorting complex required for transport III) complex with functions in the endosomal–lysosomal and the autophagic protein degradation pathway. The gene is expressed in neurons of all major brain regions. *CHMP2B* mutations were associated with enlarged vacuoles in neurons in the frontal, temporal, parietal, and occipital cortices, due to impaired endosome–lysosome fusion [54], and autophagy [55]. Ubiquitin-immunoreactive NCI do not stain for tau or TDP-43 antibodies, consistent with a pathologic classification of FTLD-UPS [2].

The clinical diagnosis of most patients in the Danish *CHMP2B* family was bvFTD, with early personality changes being the most prominent feature. In other patients, progressive aphasia involvement was described, although diagnostic criteria for PNFA, SD, or logopenic aphasia were not met. The aphasia is characterized by a reduction in spontaneous speech or mutism, while reading and repetition was conserved. The average onset age is 58 years, ranging between 46 and 65 years [53, 56]. Interestingly, rare *CHMP2B* mutations were also reported in ALS patients [55].

Mendelian ALS genes *TARDBP* and *FUS*

Mutations in *TARDBP* and *FUS* are associated with ALS. *TARDBP* mutations were initially identified as a direct consequence of the occurrence of TDP-43-derived protein species as the major constituent of the aggregates in upper and lower motor neurons of superoxide dismutase 1 (SOD1)-negative ALS patients and in FTLD-U patients [3, 4]. Subsequently, *TARDBP* mutations were identified in up to 5% of familial ALS patients. Also, in FTD-ALS and in FTLD without signs of motor neuron involvement, mutations were found [57], although here the mutation frequency is below 1% (Table 14.1).

TDP-43 is an RNA-binding protein that forms heterogeneous nuclear ribonucleoprotein complexes (hnRNP) which function in RNA processing activities, including transcription, RNA splicing, and microRNA processing. Missense mutations were found in the C-terminal glycine-rich region involved in protein–protein interactions.

Similar to *TARDBP*, *FUS* is a member of the family of hnRNP proteins. Its location in the chromosome 16p11.2 region, previously linked to ALS, made it an excellent candidate gene. Mutation analyses of *FUS* in patients of 16p11.2-linked families and other ALS families identified *FUS* mutations

[58]. Subsequently, *FUS* mutations were also detected in FTLN, although they are rare and their role in FTLN genetics remains to be established [59].

Interestingly, an accumulation of *FUS* protein in inclusion bodies in neuronal cytoplasm and nucleus was associated with three clinicopathologic subtypes of tau-negative, TDP-43-negative FTLN, defined by distinct characteristics and location of NCI and NII (FTLN-FUS) [60]. *FUS* pathologies are often associated with particular, rapidly progressing FTLN with a strong behavioral component. Atypical FTLN-U (aFTLN-U) usually has a very early-onset age in 30s or 40s and a disease duration of approximately 7 years [61]. Patients with neuronal intermediate filament inclusion disease (NIFID) usually develop the disease between 40 and 60 years of age and disease duration is on average approximately 3 years [61]. Finally, also patients with basophilic inclusion body disease (BIBD) show *FUS* immunoreactivity in frontal cortex, basal ganglia, and brainstem [60], and present with a clinical syndrome of early-onset ALS, occasionally accompanied with bvFTD [60].

Susceptibility genes and risk loci in FTLN

TMEM106B

A GWAS in 515 FTLN-TDP patients resulted in the identification of multiple single nucleotide variations (SNPs) located in a region at chromosome 7p21 containing the gene *TMEM106B* [9]. The finding was replicated in subsequent association studies [62]. The 7p21 risk haplotype was suggested to lead to increased expression of *TMEM106B* in the brain [9], although this was not replicated in another study [63]. It was suggested that *TMEM106B* may affect onset age in FTLN associated with a *GRN*

mutation by increasing granulin levels [64], possibly by modulating brain connectivity as demonstrated in asymptomatic *GRN* mutation carriers [65]. *TMEM106B* was also associated with cognitive impairment in ALS [66]. Interestingly, *TMEM106B* was also reported to be a genetic modifier in *C9orf72* repeat expansion carriers [67] by alleviating the severity of FTLN manifestation, but not of motor neuron deficits [68].

TMEM106B is a type 2 integral membrane protein localizing to late endosomes and lysosomes [69]. It may induce morphologic changes of lysosome compartments and delay the degradation of endocytic cargoes by the endolysosomal pathway [70]. A recent study demonstrated that it interacts with microtubule-associated protein 6 (MAP6) to control dendritic trafficking of lysosomes [71]. Interestingly, it was shown that inhibition of vacuolar H⁺-ATPases results in increased levels of both TMEM106B and granulin, providing a potential biochemical link [69].

Risk variations in Mendelian FTLN genes

Besides harboring Mendelian FTLN mutations, *MAPT* was associated with risk of PSP, CBS, and PD, but inconsistent results were found in FTLN [13]. *MAPT* is represented in the human population as two genetically distinct haplotypes H1 and H2 owing to its location inside a commonly inverted genomic region [72]. The H1 haplotype is overrepresented in the 4R tau disorders PSP and CBD. In young PSP patients, the risk was in part attributed to a SNP located in the large first intron of *MAPT*, which potentially modulates tau expression by modifying a LBP-1c/LSF/CP2-binding site [73]. A two-stage GWAS in 2165 PSP patients confirmed and extended these findings, and further implicated *STX6*, *EIF2AK3*, and *MOBP* in PSP [74]. Together these genes suggested roles of vesicle–membrane

fusion at the Golgi–endosomal interface, the endoplasmic reticulum unfolded protein response in PSP.

In a series of pathologically confirmed FTLD-U patients without *GRN* mutations, a common genetic variant rs5848 located in a microRNA-binding site in the 3'-untranslated region (UTR) of *GRN* was identified as risk factor for FTLD-U [75]. A significant reduction of granulin protein was observed in homozygous T-allele carriers in vivo, suggesting a similar mode of action to heterozygous loss-of-function mutations in *GRN*. Another variant in the first intron of *GRN*, potentially affecting its expression, was also reported to be associated with FTLD in another patient series [76]. Nevertheless, subsequent studies could not confirm genetic risk for FTLD associated with *GRN* variants. Further, promoter methylation plays a role in *GRN* expression and is altered in FTLD brain [77].

Pathologically expanded *C9orf72* repeat sizes usually exceed 60 units. However, the normal repeats less than 25 units were shown to have a size-dependent negative effect on gene expression [78]. Although the impact of *C9orf72* expression on development of disease remains unclear, it is of interest to note that genetic association was reported between the longer repeats within the normal size range and FTLD [78].

Concluding remarks

The clinical, pathologic, and genetic heterogeneity of FTLD has long impeded research aiming to understand underlying disease mechanisms. The strong genetic component of FTLD has significantly contributed to elucidate different aspects of this condition. We now have knowledge of the most frequently mutated genes involved in the pathogenesis of FTLD, i.e., *GRN*, *C9orf72*, and *MAPT*. These are associated with distinct neuropathologic

hallmarks, i.e., *MAPT* leads to FTLD-tau, and *GRN* and *C9orf72* are both associated with a FTLD-TDP proteinopathy, although they are each associated with distinct neuropathologic characteristics. Also, the identification of *C9orf72* has exposed novel types of inclusions resulting from expanded GGGGCC repeats. The currently known FTLD genes explain together up to 65% of familial FTLD ([Table 14.1](#)), leaving at least 35% of familial FTLD genetically unexplained. While large autosomal dominant FTLD families are available to discover additional FTLD genes, it is unlikely that other high-frequency genes will be identified. Current sequencing technologies like whole-exome and -genome sequencing will most likely identify private genes and mutations in one or a few families. Nevertheless, these rare genes can provide further insight into the pathobiology of FTLD by identifying new molecular pathways or marking key proteins in known biologic pathways.

The search for risk and protective genes for FTLD has also been greatly impeded by the clinicopathologic and underlying genetic heterogeneity. Especially, the relatively weak correlation between clinical diagnosis and underlying genetic etiologies is complicating strategies to define inclusion criteria to maximize the power of GWASs by enriching for a limited number of susceptibility genes. One GWAS used TDP-43 proteinopathy to select a more homogeneous study cohort [9], a strategy which resulted in the identification of *TMEM106B*, the first common risk gene for FTLD. Other susceptibility genes can be expected especially in SD, where family history is much less prominent than in bvFTD and PNFA. Consistent with this observation, mutations in the known FTLD genes are extremely rare in SD. Interestingly, SD is associated with a distinct type C of TDP-43 proteinopathy (see [Chapter 13](#)). FTLD-TDP type C is characterized by the presence of long DN localized in the superficial cortical layers, while NCI and NII are rare or absent compared with the

other subtypes. Together, these observations might suggest that SD is clinically, pathologically, and genetically distinct from other types of FTLD and might predominantly be caused by the interaction of multiple yet unknown risk and protective genes.

The wide range of clinical diversity associated with the Mendelian FTLD genes, i.e., onset age, FTLD clinical subtype, and motor neuron involvement, is not understood. Genetic as well as environmental modulating factors are likely to influence onset and presentation of the disease. *TMEM106B* was suggested to increase granulin protein expression and to delay disease onset. It may also modulate cognitive involvement in *C9orf72* repeat expansion carriers in the FTLD-ALS diseases. However, *TMEM106B* cannot explain the complete variance, and other modifier genes must exist. Linkage-based modifier screens in extended families and association-based studies in cohorts of patients with extreme clinical phenotypes due to the same genetic type of disease may reveal such additional modifier genes. Onset age-modifying genes might be interesting therapeutic targets, aiming at delaying onset of clinical symptoms.

With the identification of an increasing number of disease-associated genes, common disease pathways may emerge. Again the heterogeneity of FTLD suggests that a number of distinct pathways act in concert to initiate processes leading to different proteinopathies. Whether the distinct classes of FTLD-TDP proteinopathies share common downstream disease mechanisms is questionable. The fact that *C9orf72* repeat expansions are associated with both FTLD-TDP type B and type A, and that *TMEM106B* may play a role in both pathologic subtypes, suggests that the disease mechanisms of at least these FTLD-TDP subtypes converge in common pathways. Disrupted RNA and protein homeostasis and autophagy processes may represent such pathways [79]. The identification of additional rare

Mendelian FTLN genes and common susceptibility genes will be of great use to further define this and other pathways.

In conclusion, recent molecular genetics' breakthroughs have been at the basis of our growing understanding of the pathobiology of FTLN and related disorders. These emerging disease mechanisms will facilitate progress in the development of therapeutic strategies. Continued efforts to identify additional Mendelian, risk, and modifying genes will further accelerate the progress into downstream translational research. In this respect, the increasing impact of novel high-throughput molecular genetic technologies promises exciting times to come in the research of these neurodegenerative diseases.

Note

While production of this chapter was in progress, a novel Mendelian FTD gene, i.e. TANK-binding kinase 1 (*TBK1*) was discovered. *TBK1* was first identified as a novel risk gene for ALS, in which predicted damaging non-synonymous variants were significantly enriched in the exomes of > 2800 ALS patients [81]. In another exome sequencing study, *TBK1* loss-of-function mutations were identified in 9 of 252 genetically unexplained familial ALS patients, but not in > 800 control exomes [82]. Clinical evaluation of the families of the latter study indicated cognitive impairment, often progressing to FTD, in 50% of patients. A subsequent genome sequencing study of 104 FTLN-TDP patients negative for *C9orf72* and *GRN* mutations revealed four *TBK1* variations including one nonsense and three missense mutations, all with predicted damaging effect on TBK1 function [83]. Among the mutation carriers were two patients with FTLN in the absence of ALS symptoms. A targeted mutation analysis of *TBK1* in a

hospital-based cohort of 482 unrelated FTD and FTD-ALS patients and 147 ALS patients in Belgium identified 11 loss-of-function (LOF) mutation carriers, resulting in a mutation frequency 1.1% in FTD (5/460), 4.5% in FTD-ALS (1/22) and 3.4% in ALS (5/147) [84]. For several mutations, including mutations introducing a premature termination codon, in-frame deletions, and missense mutations, loss of transcript and protein was demonstrated, suggesting that the complete mutation spectrum can result in loss of TBK1 function [83, 84]. Although large genetic epidemiologic studies have not been reported yet, these early findings suggests that *TBK1* is the third most prevalent FTD gene after *C9orf72* and *GRN*, and the second most common FTD-ALS gene after *C9orf72*. Reported onset ages are between 61 and 86 years with an average of 70 years [83, 84], which is the latest of all genetic subtypes of FTD and FTD-ALS today. Pathological examinations in seven families demonstrated FTLD-TDP type B in four and type A in three families [82–84]. Given the limited information available today, it is unclear whether *TBK1* mutations can result in different pathologic FTLD-TDP subtypes, potentially modulated by other genetic factors. Alternatively, pathology data may be contaminated with observations derived from carriers of neutral *TBK1* variants with unproven loss-of-function effect.

TBK1 is an IKK-related serine/threonine protein kinase with multiple targets. It has been implemented in many biological functions including innate immune response/inflammation, autophagy, and cell proliferation. Among its targets are optineurin (OPTN) and p62, two other genes that play a role in autophagy and inflammation that have been implicated in the genetics and pathobiology of the ALS-FTD diseases [81]. Together, these findings further corroborate the central roles of these processes in FTD and ALS.

Acknowledgments

The research performed by the authors was in part funded by the Belgian Science Policy Office Interuniversity Attraction Poles Programme; the Flemish government-initiated Methusalem Excellence Program; the Alzheimer Research Foundation; the Medical Foundation Queen Elisabeth; the Research Foundation Flanders; the Agency for Innovation by Science and Technology Flanders; the University of Antwerp Research Fund, Belgium; and the MetLife Foundation (USA) Award for Medical Research to C.V.B.

References

1. Sieben A, Van Langenhove T, Engelborghs S, Martin JJ, Boon P, Cras P, *et al.* The genetics and neuropathology of frontotemporal lobar degeneration. *Acta Neuropathol* 2012;**124**(3):353–72.
2. Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, *et al.* Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol* 2010;**119**(1):1–4.
3. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, *et al.* Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;**314**(5796):130–3.
4. Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, *et al.* TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem Biophys Res Commun* 2006;**351**(3):602–11.
5. Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du Plessis D, Jaros E, *et al.* A harmonized classification system for FTLT-TDP pathology. *Acta*

Neuropathol 2011;**122**(1):111–13.

6. Neary D, Snowden J, Mann D. Frontotemporal dementia. *Lancet Neurol* 2005;**4**(11):771–80.

7. Cruts M, Theuns J, Van Broeckhoven C. Locus-specific mutation databases for neurodegenerative brain diseases. *Hum Mutat* 2012;**33**(9):1340–4.

8. Van Langenhove T, van der Zee J, Van Broeckhoven C. The molecular basis of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum. *Ann Med* 2012;**44**(8):817–28.

9. Van Deerlin V, Sleiman PM, Martinez-Lage M, Chen-Plotkin A, Wang LS, Graff-Radford NR, *et al.* Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. *Nat Genet* 2010;**42**(3):234–9.

10. Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S, *et al.* Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. *Ann Neurol* 1997;**41**(6):706–15.

11. Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, *et al.* Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998;**393**(6686):702–5.

12. D'Souza I, Schellenberg GD. Tau exon 10 expression involves a bipartite intron 10 regulatory sequence and weak 5' and 3' splice sites. *J Biol Chem* 2002;**277**(29):26587–99.

13. Rademakers R, Cruts M, Van Broeckhoven C. The role of tau (*MAPT*) in frontotemporal dementia and related tauopathies. *Hum Mutat* 2004;**24**(4):277–95.

14. Cruts M, Van Broeckhoven C. Loss of progranulin function in frontotemporal lobar degeneration. *Trends Genet* 2008;**24**(4):186–94.

-
- 15.** Josephs KA, Hodges JR, Snowden JS, Mackenzie IR, Neumann M, Mann DM, *et al.* Neuropathological background of phenotypical variability in frontotemporal dementia. *Acta Neuropathol* 2011;**122**(2):137–53.
-
- 16.** Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, *et al.* Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* 2006;**442**(7105):916–19.
-
- 17.** Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, *et al.* Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature* 2006;**442**(7105):920–4.
-
- 18.** Kleinberger G, Capell A, Haass C, Van Broeckhoven C. Mechanisms of granulin deficiency: lessons from cellular and animal models. *Mol Neurobiol* 2013;**47**(1):337–60.
-
- 19.** Brouwers N, Sleegers K, Engelborghs S, Maurer-Stroh S, Gijselinck I, van der Zee J, *et al.* Genetic variability in progranulin contributes to risk for clinically diagnosed Alzheimer disease. *Neurology* 2008;**71**(9):656–64.
-
- 20.** Sleegers K, Brouwers N, Van Broeckhoven C. Role of progranulin as a biomarker for Alzheimer's disease. *Biomark Med* 2010;**4**(1):37–50.
-
- 21.** Sleegers K, Brouwers N, Maurer-Stroh S, van Es MA, Van Damme P, Van Vught PW, *et al.* Progranulin genetic variability contributes to amyotrophic lateral sclerosis. *Neurology* 2008;**71**(4):253–9.
-
- 22.** Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. *Curr Opin Neurol* 2011;**24**(6):542–9.
-
- 23.** Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, *et al.* Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. *Brain* 2008;**131**(Pt 3):732–46.

-
- 24.** Brouwers N, Nuytemans K, van der Zee J, Gijselinck I, Engelborghs S, Theuns J, *et al.* Alzheimer and Parkinson diagnoses in progranulin null mutation carriers in an extended founder family. *Arch Neurol* 2007;**64**(10):1436–46.
-
- 25.** Chen-Plotkin AS, Martinez-Lage M, Sleiman PM, Hu W, Greene R, Wood EM, *et al.* Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. *Arch Neurol* 2011;**68**(4):488–97.
-
- 26.** Rademakers R, Baker M, Gass J, Adamson J, Huey ED, Momeni P, *et al.* Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C→T (Arg493X) mutation: an international initiative. *Lancet Neurol* 2007;**6**(10):857–68.
-
- 27.** Vance C, Al Chalabi A, Ruddy D, Smith BN, Hu X, Sreedharan J, *et al.* Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2–21.3. *Brain* 2006;**129**(Pt 4):868–76.
-
- 28.** Morita M, Al Chalabi A, Andersen PM, Hosler B, Sapp P, Englund E, *et al.* A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology* 2006;**66**(6):839–44.
-
- 29.** Laaksovirta H, Peuralinna T, Schymick JC, Scholz SW, Lai SL, Myllykangas L, *et al.* Chromosome 9p21 in amyotrophic lateral sclerosis in Finland: a genome-wide association study. *Lancet Neurol* 2010;**9**(10):978–85.
-
- 30.** DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;**72**(2):245–56.
-
- 31.** Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;**72**(2):257–68.

32. Gijselinck I, Van Langenhove T, van der Zee J, Sleegers K, Philtjens S, Kleinberger G, *et al.* A *C9orf72* promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. *Lancet Neurol* 2012;**11**(1):54–65.

33. Cruts M, Gijselinck I, Van Langenhove T, van der Zee J, Van Broeckhoven C. Current insights into the *C9orf72* repeat expansion diseases of the FTLD/ALS spectrum. *Trends Neurosci* 2013;**36**(8):450–9.

34. Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, *et al.* Frequency of the *C9orf72* hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol* 2012;**11**(4):323–30.

35. Smith BN, Newhouse S, Shatunov A, Vance C, Topp S, Johnson L, *et al.* The *C9ORF72* expansion mutation is a common cause of ALS+/-FTD in Europe and has a single founder. *Eur J Hum Genet* 2013;**21**(1):102–8.

36. Beck J, Poulter M, Hensman D, Rohrer JD, Mahoney CJ, Adamson G, *et al.* Large *C9orf72* hexanucleotide repeat expansions are seen in multiple neurodegenerative syndromes and are more frequent than expected in the UK population. *Am J Hum Genet* 2013;**92**(3):345–53.

37. Abel O, Powell JF, Andersen PM, Al-Chalabi A. ALSod: a user-friendly online bioinformatics tool for amyotrophic lateral sclerosis genetics. *Hum Mutat* 2012;**33**(9):1345–51.

38. Mackenzie IR, Frick P, Neumann M. The neuropathology associated with repeat expansions in the *C9ORF72* gene. *Acta Neuropathol* 2014;**127**(3):347–57.

39. Mori K, Lammich S, Mackenzie IR, Forne I, Zilow S, Kretschmar H, *et al.* hnRNP A3 binds to GGGGCC repeats and is a constituent of p62-

positive/TDP43-negative inclusions in the hippocampus of patients with *C9orf72* mutations. *Acta Neuropathol* 2013;**125**(3):413–23.

40. Mori K, Weng SM, Arzberger T, May S, Rentzsch K, Kremmer E, *et al.* The *C9orf72* GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTLN/ALS. *Science* 2013;**339**(6125):1335–8.

41. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, *et al.* Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. *Brain* 2012;**135**(Pt 3):693–708.

42. Murray ME, DeJesus-Hernandez M, Rutherford NJ, Baker M, Duara R, Graff-Radford NR, *et al.* Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in C9ORF72. *Acta Neuropathol* 2011;**122**(6):673–90.

43. Van Langenhove T, van der Zee J, Gijselinck I, Engelborghs S, Vandenberghe R, Vandenbulcke M, *et al.* Distinct clinical characteristics of *C9orf72* expansion carriers compared with *GRN*, *MAPT*, and nonmutation carriers in a Flanders-Belgian FTLN cohort. *JAMA Neurol* 2013;**70**(3):365–73.

44. Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, Pedraza O, *et al.* Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in *C9ORF72*. *Brain* 2012;**135**(Pt 3):765–83.

45. Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, *et al.* Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat Genet* 2004;**36**(4):377–81.

46. Weihl CC, Pestronk A, Kimonis VE. Valosin-containing protein disease: inclusion body myopathy with Paget's disease of the bone and fronto-temporal

dementia. *Neuromuscul Disord* 2009;**19**(5):308–15.

47. Dai RM, Li CC. Valosin-containing protein is a multi-ubiquitin chain-targeting factor required in ubiquitin-proteasome degradation. *Nat Cell Biol* 2001;**3**(8):740–4.

48. Ju JS, Weihl CC. p97/VCP at the intersection of the autophagy and the ubiquitin proteasome system. *Autophagy* 2010;**6**(2):283–5.

49. Schroder R, Watts GD, Mehta SG, Evert BO, Broich P, Fliesbach K, *et al.* Mutant valosin-containing protein causes a novel type of frontotemporal dementia. *Ann Neurol* 2005;**57**(3):457–61.

50. Weihl CC. Valosin containing protein associated fronto-temporal lobar degeneration: clinical presentation, pathologic features and pathogenesis. *Curr Alzheimer Res* 2011;**8**(3):252–60.

51. Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, *et al.* Exome sequencing reveals *VCP* mutations as a cause of familial ALS. *Neuron* 2010;**68**(5):857–64.

52. Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich H, *et al.* Mutations in the endosomal ESCRTIII-complex subunit *CHMP2B* in frontotemporal dementia. *Nat Genet* 2005;**37**(8):806–8.

53. van der Zee J, Urwin H, Engelborghs S, Bruyland M, Vandenberghe R, Dermaut B, *et al.* *CHMP2B* C-truncating mutations in frontotemporal lobar degeneration are associated with an aberrant endosomal phenotype *in vitro*. *Hum Mol Genet* 2008;**17**(2):313–22.

54. Urwin H, Authier A, Nielsen JE, Metcalf D, Powell C, Froud K, *et al.* Disruption of endocytic trafficking in frontotemporal dementia with *CHMP2B* mutations. *Hum Mol Genet* 2010;**19**(11):2228–38.

55. Cox LE, Ferraiuolo L, Goodall EF, Heath PR, Higginbottom A, Mortiboys

H, *et al.* Mutations in *CHMP2B* in lower motor neuron predominant amyotrophic lateral sclerosis (ALS). *PLoS One* 2010;**5**(3):e9872.

56. Isaacs AM, Johannsen P, Holm I, Nielsen JE. Frontotemporal dementia caused by *CHMP2B* mutations. *Curr Alzheimer Res* 2011;**8**(3):246–51.

57. Borroni B, Bonvicini C, Alberici A, Buratti E, Agosti C, Archetti S, *et al.* Mutation within *TARDBP* leads to frontotemporal dementia without motor neuron disease. *Hum Mutat* 2009;**30**(11):E974–83.

58. Kwiatkowski TJ, Jr., Bosco DA, Leclerc AL, Tamrazian E, Vandenburg CR, Russ C, *et al.* Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science* 2009;**323**(5918):1205–8.

59. Van Langenhove T, van der Zee J, Sleegers K, Engelborghs S, Vandenberghe R, Gijselinck I, *et al.* Genetic contribution of *FUS* to frontotemporal lobar degeneration. *Neurology* 2010;**74**(5):366–71.

60. Mackenzie IR, Munoz DG, Kusaka H, Yokota O, Ishihara K, Roeber S, *et al.* Distinct pathological subtypes of FTL-D-FUS. *Acta Neuropathol* 2011;**121**(2):207–18.

61. Lashley T, Rohrer JD, Bandopadhyay R, Fry C, Ahmed Z, Isaacs AM, *et al.* A comparative clinical, pathological, biochemical and genetic study of fused in sarcoma proteinopathies. *Brain* 2011;**134**(Pt 9):2548–64.

62. van der Zee J, Van Broeckhoven C. *TMEM106B* a novel risk factor for frontotemporal lobar degeneration. *J Mol Neurosci* 2011;**45**(3):516–21.

63. van der Zee J, Van Langenhove T, Kleinberger G, Sleegers K, Engelborghs S, Vandenberghe R, *et al.* *TMEM106B* is associated with frontotemporal lobar degeneration in a clinically diagnosed patient cohort. *Brain* 2011;**134**(3):808–15.

64. Cruchaga C, Graff C, Chiang HH, Wang J, Hinrichs AL, Spiegel N, *et al.* Association of *TMEM106B* gene polymorphism with age at onset in granulin

mutation carriers and plasma granulin protein levels. *Arch Neurol* 2011;**68**(5):581–6.

65. Premi E, Formenti A, Gazzina S, Archetti S, Gasparotti R, Padovani A, *et al.* Effect of *TMEM106B* polymorphism on functional network connectivity in asymptomatic *GRN* mutation carriers. *JAMA Neurol* 2014;**71**(2):216–21.

66. Vass R, Ashbridge E, Geser F, Hu WT, Grossman M, Clay-Falcone D, *et al.* Risk genotypes at *TMEM106B* are associated with cognitive impairment in amyotrophic lateral sclerosis. *Acta Neuropathol* 2011;**121**(3):373–80.

67. van Blitterswijk M, Mullen B, Nicholson AM, Bieniek KF, Heckman MG, Baker MC, *et al.* *TMEM106B* protects *C9ORF72* expansion carriers against frontotemporal dementia. *Acta Neuropathol* 2014;**127**(3):397–406.

68. Gallagher MD, Suh E, Grossman M, Elman L, McCluskey L, van Swieten JC, *et al.* *TMEM106B* is a genetic modifier of frontotemporal lobar degeneration with *C9orf72* hexanucleotide repeat expansions. *Acta Neuropathol* 2014;**127**(3):407–18.

69. Lang CM, Fellerer K, Schwenk BM, Kuhn PH, Kremmer E, Edbauer D, *et al.* Membrane orientation and subcellular localization of transmembrane protein 106B (TMEM106B), a major risk factor for frontotemporal lobar degeneration. *J Biol Chem* 2012;**287**(23):19355–65.

70. Brady OA, Zheng Y, Murphy K, Huang M, Hu F. The frontotemporal lobar degeneration risk factor, TMEM106B, regulates lysosomal morphology and function. *Hum Mol Genet* 2013;**22**(4):685–95.

71. Schwenk BM, Lang CM, Hogg S, Tahirovic S, Orozco D, Rentzsch K, *et al.* The FTL risk factor TMEM106B and MAP6 control dendritic trafficking of lysosomes. *EMBO J* 2014;**33**(5):450–67.

72. Cruts M, Rademakers R, Gijselinck I, van der Zee J, Dermaut B, De Pooter T, *et al.* Genomic architecture of human 17q21 linked to frontotemporal

dementia uncovers a highly homologous family of low copy repeats in the tau region. *Hum Mol Genet* 2005;**14**(13):1753–62.

73. Rademakers R, Melquist S, Cruts M, Theuns J, Del Favero J, Poorkaj P, *et al.* High-density SNP haplotyping suggests altered regulation of tau gene expression in progressive supranuclear palsy. *Hum Mol Genet* 2005;**14**(21):3281–92.

74. Hoglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, *et al.* Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. *Nat Genet* 2011;**43**(7):699–705.

75. Rademakers R, Eriksen JL, Baker M, Robinson T, Ahmed Z, Lincoln SJ, *et al.* Common variation in the miR-659 binding-site of *GRN* is a major risk factor for TDP43-positive frontotemporal dementia. *Hum Mol Genet* 2008;**17**(23):3631–42.

76. Galimberti D, Fenoglio C, Cortini F, Serpente M, Venturelli E, Villa C, *et al.* *GRN* variability contributes to sporadic frontotemporal lobar degeneration. *J Alzheimers Dis* 2010;**19**(1):171–7.

77. Banzhaf-Strathmann J, Claus R, Mucke O, Rentzsch K, van der Zee J, Engelborghs S, *et al.* Promoter DNA methylation regulates progranulin expression and is altered in FTLN. *Acta Neuropathol Commun* 2013;**1**(1):16.

78. van der Zee J, Gijssels I, Dillen L, Van Langenhove T, Theuns J, Engelborghs S, *et al.* A pan-European study of the *C9orf72* repeat associated with FTLN: geographic prevalence, genomic instability and intermediate repeats. *Hum Mutat* 2013;**34**(2):363–73.

79. Janssens J, Van Broeckhoven C. Pathological mechanisms underlying TDP-43 driven neurodegeneration in FTLN-ALS spectrum disorders. *Hum Mol Genet* 2013;**22**(R1):R77–7.

80. Gijssels I, Van Broeckhoven C, Cruts M. Granulin mutations associated

with frontotemporal lobar degeneration and related disorders: an update. *Hum Mutat* 2008;**29**(12):1373–86.

81. Cirulli ET, Lasseigne BN, Petrovski S, Sapp PC, Dion PA, Leblond CS, *et al.* Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. *Science* 2015;**347**(6229):1436–41.

82. Freischmidt A, Wieland T, Richter B, Ruf W, Schaeffer V, Muller K, *et al.* Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia. *Nat Neurosci* 2015;**18**(5):631–6.

83. Pottier C, Bieniek KF, Finch N, van de Vorst M, Baker M, Perkersen R, *et al.* Whole-genome sequencing reveals important role for TBK1 and OPTN mutations in frontotemporal lobar degeneration without motor neuron disease. *Acta Neuropathol* 2015;**130**(1):77–92.

84. Gijselinck I, Van Mossevelde S, van der Zee J, Sieben A, Philtjens S, Heeman B, *et al.* Loss of TBK1 is a frequent cause of frontotemporal dementia in a Belgian cohort. *Neurology* 2015. In press.

Chapter 15

Pathophysiology and animal models of frontotemporal dementia



Brian A. Warmus and Erik D. Roberson

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

The past decade has been very exciting for frontotemporal dementia (FTD), as a series of new molecules has been implicated in its pathogenesis. Ongoing studies in cell and animal models are unraveling some of the mysteries of FTD and many of the underlying mechanisms are becoming clearer. At the same time, different cellular pathways and processes have been implicated and the pathophysiology of FTD may be as heterogeneous as the clinical syndromes and neuropathologic forms are.

There are generally two primary sources of information about the molecular causes of human neurologic diseases: genetics and pathology. This is certainly true in FTD. As detailed in [Chapter 14](#), the three common genetic causes of FTD are mutations in *C9orf72* (chromosome 9 open reading frame 72), *MAPT* (tau), and *GRN* (progranulin), while mutations in

VCP (valosin-containing protein), *CHMP2B* (charged multivesicular protein 2B), *TARDBP* (transactive response DNA-binding protein 43[TDP-43]), and *FUS* (fused in sarcoma) are minor forms ([Table 15.1](#)). And as detailed in [Chapter 13](#), the main pathologic forms of FTD are characterized by accumulation of TDP-43, tau, or FUS ([Table 15.1](#)). These are the molecules we will consider in this chapter.

Table 15.1 Genetic and neuropathologic causes of FTD

	Genetics	Neuropathology
Most common	<i>C9orf72</i>	TDP-43
	<i>MAPT</i> (tau)	Tau
	<i>GRN</i> (progranulin)	
Others	<i>VCP</i>	
	<i>CHMP2B</i>	
	<i>TARDBP</i> (TDP-43)	FUS
	<i>FUS</i>	

C9ORF72

C9ORF72 is the newest addition to the roster of causative molecules in FTD. In 2011, expansions of a GGGGCC hexanucleotide repeat in *C9orf72* were found to cause FTD [[1](#), [2](#)]. Normal alleles usually contain only two of these repeats, and rarely more than 15 repeats [[3](#)], while disease-associated alleles contain more than 30 repeats, commonly hundreds or thousands. Patients with *C9orf72* mutations can develop behavioral variant FTD (bvFTD), amyotrophic lateral sclerosis (ALS), or FTD-ALS, although other clinical subtypes are also seen and mutation carriers can also develop other neurodegenerative disorders.

Pathophysiology

Three main theories for the pathogenicity of the GGGGCC repeat expansion have been investigated.

First, the expansion is associated with reduced levels of some *C9orf72* transcripts [1, 4], suggesting possible loss of function. The repeat expansion is located near the promoter of the gene, and several loss-of-function mechanisms have been proposed. Epigenetic changes, including DNA methylation at CpG sites in the repeat [5] and histone methylation [6], have been reported and could contribute to downregulation of transcription.

Another possibility relates to a unique secondary structure, called a G-quadruplex, formed in guanine-rich nucleic acids, including the GGGGCC repeats in *C9orf72* (Figure 15.1A–C). These structures, which are based on hydrogen bonding between guanine nucleotides, occur especially in regulatory regions and may regulate transcription. In *C9orf72*, the formation of G-quadruplex in the sense DNA strand leaves the antisense strand exposed to more stable interactions with the nascent transcribed RNA [7]. The resulting DNA•RNA hybrid, called an R loop, aborts transcription, resulting in a series of truncated transcripts and reduced levels of the full-length transcript (Figure 15.1D (1)).

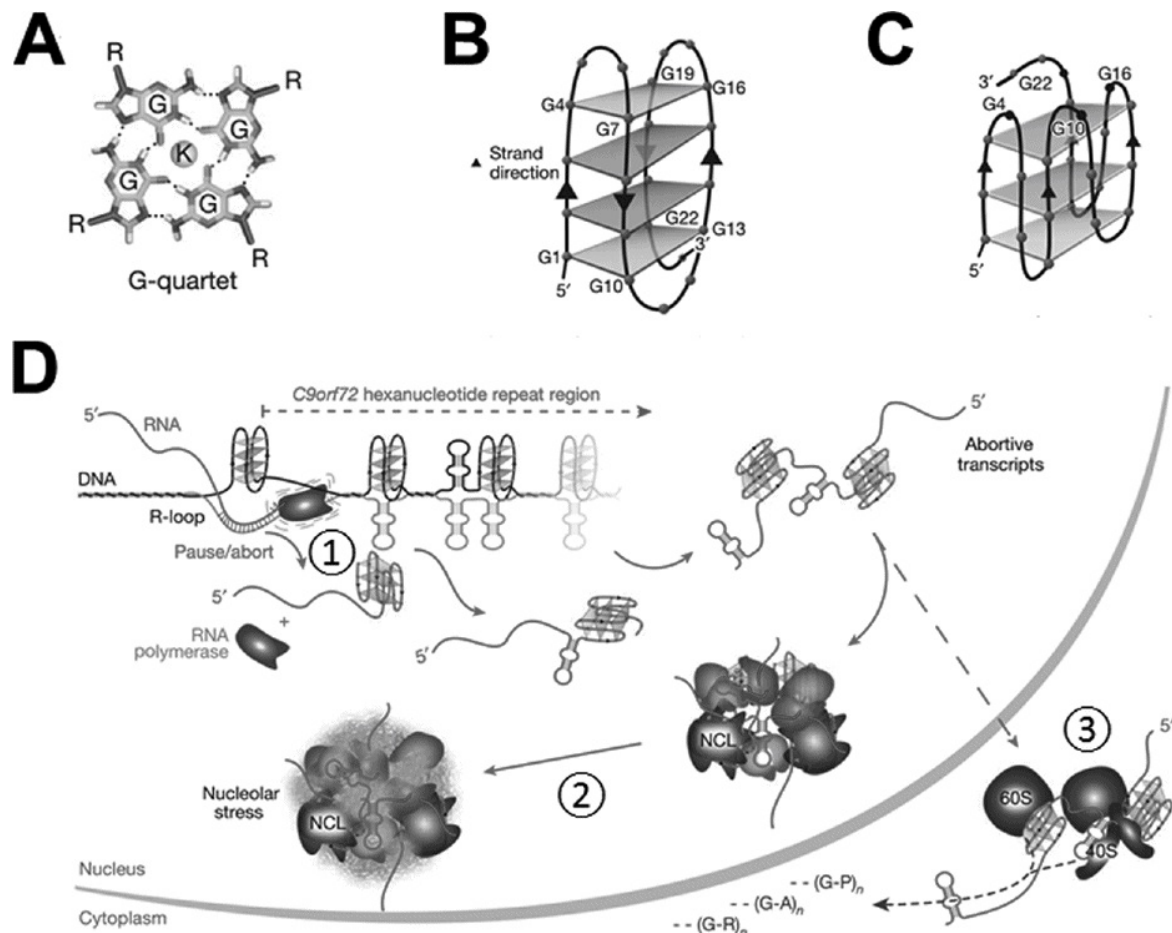


Figure 15.1 G-quadruplex structures and *C9orf72* pathophysiology. (A) Hydrogen bonds between four guanine residues can form a planar structure called a G-quartet. (B,C) G-quartets (gray rectangles) stack together in a G-quadruplex, either with antiparallel strands (B), which may form in GGGGCC DNA, or parallel strands (C), which may form in GGGGCC RNA. (D) Model showing how repeat expansion can be associated with both loss of *C9orf72* transcription (1), formation of toxic RNA foci involving nucleolin (NCL) (2), and repeat-associated non-ATG (RAN) translation of dipeptide repeats (3).

Adapted and reprinted, with permission, from Haeusler AR, Donnelly CJ, Periz G, *et al.* (2014). *C9orf72* nucleotide repeat structures initiate molecular cascades of disease. *Nature*, 507, 195–200.

Second, patients with *C9orf72* mutations develop focal RNA aggregates termed RNA foci that may sequester important RNA-binding proteins, causing toxicity due to an RNA gain of function. Similar

mechanisms occur in other repeat expansion disorders, including myotonic dystrophy. The GGGGCC repeat has been shown to bind several proteins. In *Drosophila*, the repeats sequester Pur α , and neurotoxicity can be rescued by overexpressing Pur α [8]. In addition, RNA transcripts containing the GGGGCC repeat also form G-quadruplexes, and these structures bind nucleolin, a major protein in the nucleolus, which is responsible for ribosome assembly and translation [7]. Thus, RNA foci may sequester proteins critical for normal RNA processing and translation (Figure 15.1D (2)).

Finally, the expansion can be translated into an aberrant dipeptide repeat, possibly causing toxic gain of function at the protein level (Figure 15.1D (3)). Another unique cell biologic process appears to be involved, called repeat-associated non-ATG (RAN) translation. As the name implies, RAN translation does not require the typical ATG codon as a translation start site, and leads to formation of homopolymeric (for triplet repeats) or dipeptide repeat peptides (for hexanucleotide repeats). In patients with C9 expansions, there is RAN translation of both sense and antisense transcripts, leading to formation of poly(GP), poly(GA), and poly(GR) from the sense strand and poly(PR) and poly(PA) from the antisense strand [9–11]. Accumulations of these aggregated dipeptide polymers is characteristic in neuropathologic specimens from *C9orf72* repeat expansion carriers, although it is not yet clear whether the aggregates are pathogenic or not.

Animal models

A few early animal models of C9ORF72 have been described. In initial approaches to determining whether loss of C9ORF72 has detrimental effects, knockdown of the zebra fish C9ORF72 homologue (zC9orf72), caused axonopathy and swimming deficits [4], but antisense knockdown of

C9orf72 in mice had no discernible effect [12]. Meanwhile, expressing GGGGCC(n) repeats in either *Drosophila* or zebra fish caused toxicity, with RNA foci in the zebra fish model [8, 13]. Thus, the early animal work provides tentative support for both loss-of-function and gain-of-function hypotheses. A host of new models now under development, including transgenic and knockout mice, should help resolve these issues.

Tau

Tau is unique in that it is both a common genetic cause of FTD and a common neuropathologic substrate. The clinical term for cases with tau mutations is frontotemporal dementia and parkinsonism linked to chromosome 17, tau gene (FTDP-17 *MAPT*). The neuropathologic term is FTLD-tau. These conditions overlap, in that FTDP-17 *MAPT* patients have FTLD-tau neuropathology [14]. Tau-associated FTD can manifest as many different clinical subtypes, although the semantic variant of primary progressive aphasia (PPA) and FTD-ALS are much less common with tau and are more associated with TDP-43.

Pathophysiology

Mutations in the *MAPT* gene on chromosome 17q21.1 were the first genetic cause of FTD to be identified [15–17]. Since the first tau mutation discovery, there have been over 40 tau mutations found to cause FTD [18]. Not all FTD-associated tau mutations are alike. Mutations can affect tau at the protein level or pre-mRNA level.

At the protein level, most tau mutations are missense and are clustered in the microtubule-binding domains, which may interfere with interactions with microtubules. A few other missense mutations are outside the

microtubule-binding domain at the amino- and carboxy-termini of tau. While tau is mostly unstructured, the termini tend to fold back toward the microtubule-binding domains, which may allow these termini mutations to interfere with microtubule binding. Mutations such as G272V, P301L, V337M, and R406W make tau more prone to hyperphosphorylation [19] and R5L, K257T, I260V, G272V, ΔK280, P301L, P301S, Q336R, V337M, and R406W mutations make tau more prone to aggregation.

At the pre-mRNA level, some missense, silent, or intronic mutations cause alternative splicing of exon 10. Tau can be alternatively spliced to generate six isoforms, including three isoforms that have three microtubule-binding domains (3R) and three isoforms that have four microtubule-binding domains (4R). Inclusion of exon 10 drives formation of 4R tau. Most mutations affecting alternative splicing, such as N279K, L284L, ΔN296, N296N, N296H, P301S, G303V, S305N, S305S, S305I, E10+3, E10+11, E10+12, E10+13, E10+14, E10+16, and E342V, promote the inclusion of exon 10, causing more 4R tau [20]. Other mutations, such as L266V, E9+33, G272V, ΔK280, E10+19, and E10+29, promote exclusion of exon 10, causing more 3R tau [20]. 3R tau has less binding affinity for microtubules and is less efficient at promoting microtubule assembly [21]. Some missense mutations are in exon 10 and therefore only appear if exon 10 is included in the three isoforms of 4R tau.

Tau aggregates in FTLD-tau are made up of post-translationally modified tau. Tau can be modified by hyperphosphorylation, ubiquitination, acetylation, nitration, and glycosylation. Hyperphosphorylation of tau is thought to cause a loss of function as phosphorylation decreases the binding of tau to microtubules, which leads to microtubule destabilization.

The type of FTLD-tau aggregates can sometimes distinguish between clinical syndromes of FTD. 3R tau aggregates (Pick bodies) are found in Pick's disease (PiD). 4R tau aggregates are found in progressive

supranuclear palsy (PSP), corticobasal degeneration (CBD), and argyrophilic grain disease (AGD). A mix of 3R and 4R tau is more common and is found in bvFTD and PPA cases.

Animal models

Since FTLD-tau makes up 45% of FTD cases and tau mutations are one of the major genetic causes of FTD, researchers have developed over 25 transgenic mouse models expressing either wild-type or mutant tau to try to recapitulate and understand the pathophysiology of tau.

The first transgenic mouse models expressed wild-type human tau as either the shortest 3R isoform [22] or the longest 4R isoform of tau [23]. In both models, tau was hyperphosphorylated and localized to the somatodendritic compartment, but there were no neurofibrillary tangle (NFT)-like aggregates. Later models increased wild-type human tau expression under different promoters and this led to axonal degeneration [24, 25] and NFT-like aggregates at 18–20 months of age [26], recapitulating some facets of FTLD-tau neuropathology. In another model, overexpression of wild-type tau caused cell loss several months prior to the detection of NFT-like aggregates [27]. These data were the first to suggest that NFT-like aggregates might not be the cause of cell death.

To better understand how tau causes cell death, transgenic mouse models expressing mutant human tau soon followed. Mutant tau (either P301L [28–30] or P301S [31]) was hyperphosphorylated, formed NFT-like aggregates, and caused neuron loss. One of these models, rTg4510 (P301L), further dissociated NFT-like aggregates and cell loss [30, 32]. When the mutant tau transgene was suppressed, NFT-like aggregates continued forming, but cell numbers stabilized and cognition improved. Interestingly, neurons that formed NFT-like aggregates seemed to be less likely to undergo

cell death in rTg4510 mice [33]. Additionally, the ultrastructure of cells with NFT-like aggregates appears healthier than that of cells without [34]. On the contrary, a proaggregation mutant tau (Δ K280) causes cell death while mutations that prevent tau aggregation prevent cell death [35]. The most likely hypothesis to explain all of these data is that small, soluble tau oligomers, but not the large, NFT-like aggregates detectable by light microscopy, are responsible for cell death.

Interestingly, functional deficits (synaptic and cognitive deficits) appear independent of NFT-like aggregates and cell death. Neurons with NFT-like aggregates can remain functionally intact [36] and are functionally similar to neurons without aggregates [37]. Synapse loss and cognitive deficits can precede NFT-like aggregates by several months [38]. Most convincingly, in two mouse models where the mutant tau transgene can be turned off, NFT-like aggregates and cell death persist while synaptic and cognitive deficits are reversed [30, 35, 39]. Loss of synapses and/or impaired synaptic transmission coincides with cognitive deficits. In fact, mislocalization of tau to the synapse impairs synaptic transmission before loss of synapses occurs (Figure 15.2A–B) [40] and when synapse loss eventually occurs, it is independent of whether the neurons have NFT-like aggregates (Figure 15.2C) [37]. Research focusing on how tau affects synaptic proteins and synaptic transmission will likely provide potential treatment targets for restoring cognition.

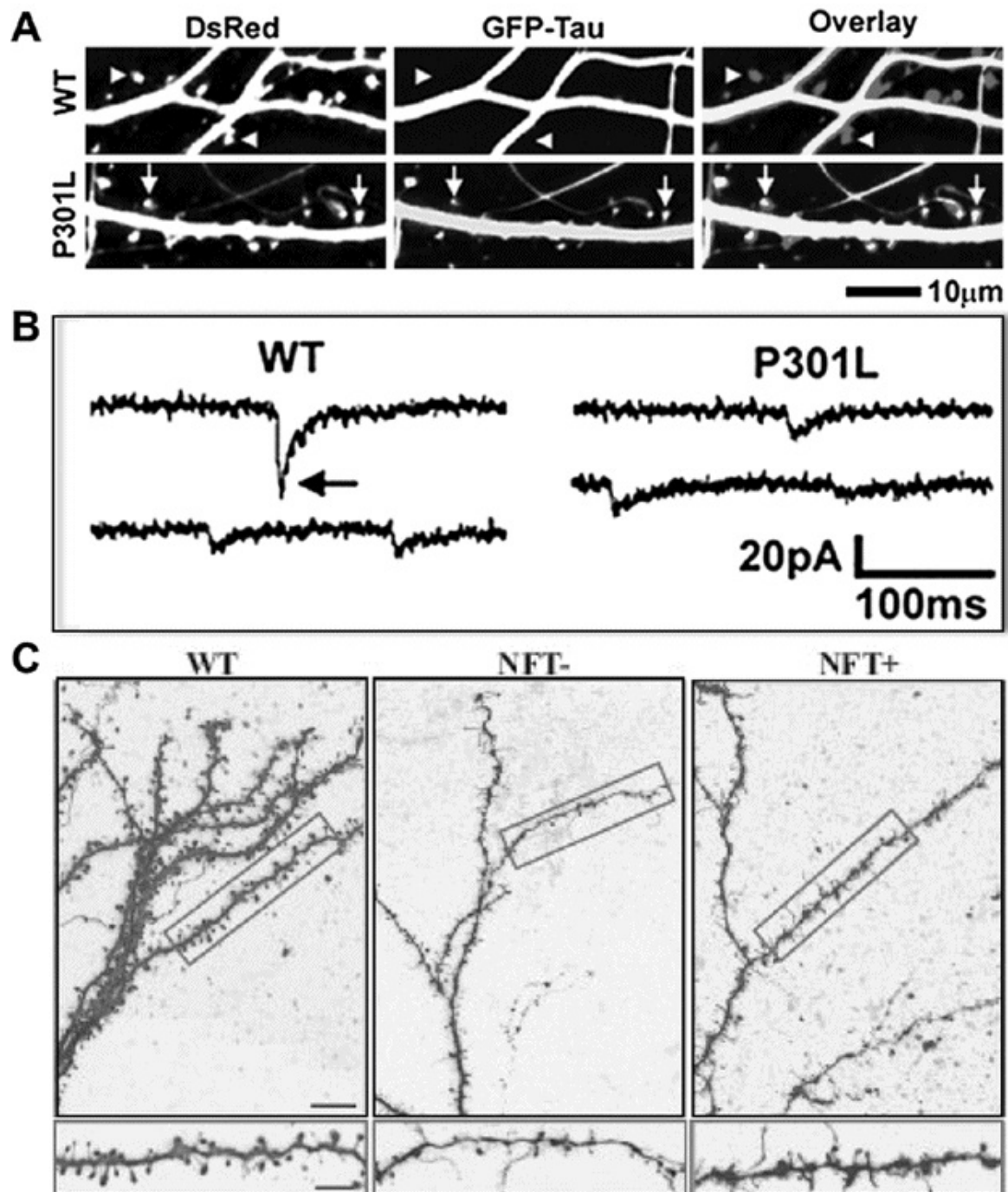


Figure 15.2 Small, soluble tau, not neurofibrillary tangles, is responsible for neuronal deficits. **(A)** Dissociated rat hippocampal neurons coexpressing DsRed (to label dendrites and spines) and either wild-type (WT) or mutant (P301L) tau tagged with GFP. Overlap of tau is present in dendrites and spines. In wild-type neurons, most dendritic spines have no tau (triangles), while in neurons from rTg4510 mice, most spines contain mutant tau (arrows). There is no difference in spine density. **(B)** Representative miniature excitatory postsynaptic current (mEPSC) recordings from neurons in (A). mEPSCs are

smaller and less frequent in neurons with P301L mutant tau. Given no difference in spine density, these data suggest mislocalized tau in dendritic spines causes synaptic deficits. (A–B) Reprinted with permission from Hoover BR, Reed MN, Su J, *et al.* (2010). Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. *Neuron*, 68, 1067–81. (C) Layer III frontal cortex pyramidal neurons from 8.5-month-old rTg4510 (P301L mutant) mice labeled with biocytin and fluorescently stained. Neurons were also co-stained for neurofibrillary tangles (NFTs) with thioflavin-S. Dendritic spine density is decreased in mutant tau mice, but there is no difference between neurons with or without NFTs, suggesting spine loss is independent of NFTs.

Reprinted with permission from Rocher AB, Crimins JL, Amatrudo JM, *et al.* (2010). Structural and functional changes in tau mutant mice neurons are not linked to the presence of NFTs. *Experimental Neurology*, 223, 385–93.

Besides impairing synaptic function, tau appears to utilize the synapse to trans-synaptically spread tau pathology to anatomically connected regions. With increasing synaptic activity, tau is released into the extracellular space ([Figure 15.3A–B](#)) [[41](#)]. Neurons can internalize extracellular tau via bulk endocytosis [[42–45](#)], transport tau anterograde and retrograde via endosomal vesicles ([Figure 15.3C–D](#)) [[45](#)], and spread tau pathology to anatomically connected regions [[46–48](#)]. FTD causes region-specific atrophy and reduced connectivity in the salience network [[49–52](#)], which consists of functionally and anatomically connected brain regions. The selective vulnerability of these anatomically connected networks is likely due to trans-synaptic spread [[53](#)]. Research focusing on how tau is released, endocytosed, and transported could provide potential treatment targets to slow the spread of pathologic tau and, possibly, slow the progression of FTD.

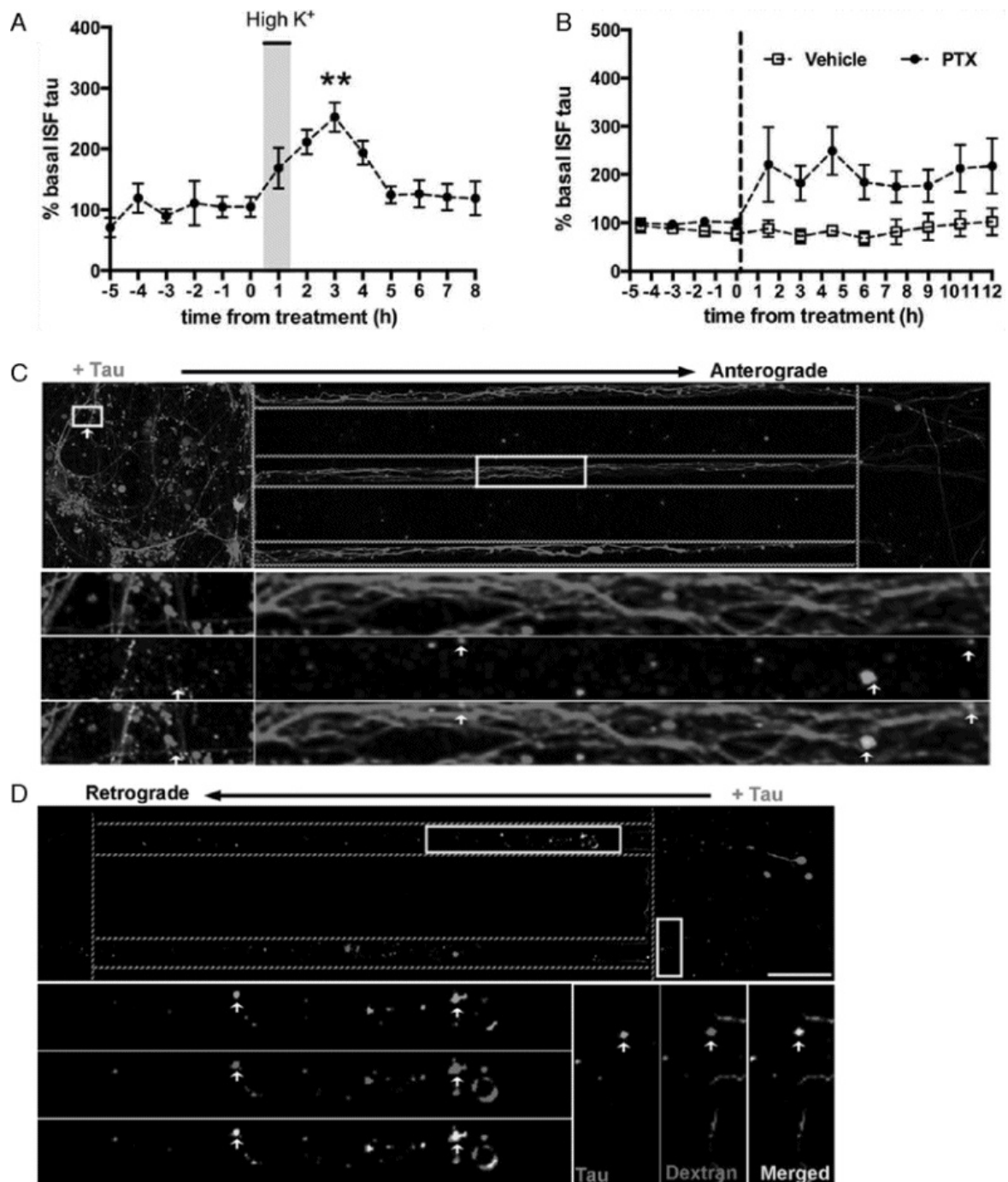


Figure 15.3 Tau can spread from neuron to neuron. (A) In vivo microdialysis measurements in hippocampus from awake and moving wild-type mice. Increasing neuronal activity by depolarization with high K^+ (shaded area) causes increased levels of tau in the interstitial fluid (ISF). (B) Increasing neuronal activity by blocking inhibitory signaling with picrotoxin (PTX) causes increased levels of tau in ISF. (A–B) Reprinted with permission from Yamada K, Holth JK, Liao F, *et al.* (2014). Neuronal activity regulates extracellular tau in vivo. *Journal of Experimental Medicine*, 211, 387–93. (C)

Microfluidic chambers with cultured neurons compartmentalized into somatodendritic (left), axon shafts (middle), and axon terminals (right). Dotted lines designate chamber separations. Neurons are stained with DAPI (blue) for nuclei and anti- β -tubulin (red) for dendrites and axons. When low-molecular-weight tau (green) is added to the somatodendritic compartment, neurons internalize tau and transport it toward the axon terminals. Also (not shown here), tau co-localizes with markers of endocytosis, dextran, and Rab5, and tau's uptake is blocked by the endocytosis inhibitor, Dynasore. **(D)** When tau (green) is added to the axon terminal compartment, tau undergoes endocytosis and retrograde transport down the axon shafts toward the cell bodies. Here, tau co-localizes with dextran (red), a marker of endocytosis. (C–D) Multiple insets show higher magnification of selected areas.

Reprinted with permission from Wu JW, Herman M, Liu L, *et al.* (2013).

Small misfolded Tau species are internalized via bulk endocytosis and anterogradely and retrogradely transported in neurons. *Journal of Biological Chemistry*, 288, 1856–70. [For the color version please refer to the plate section.](#)

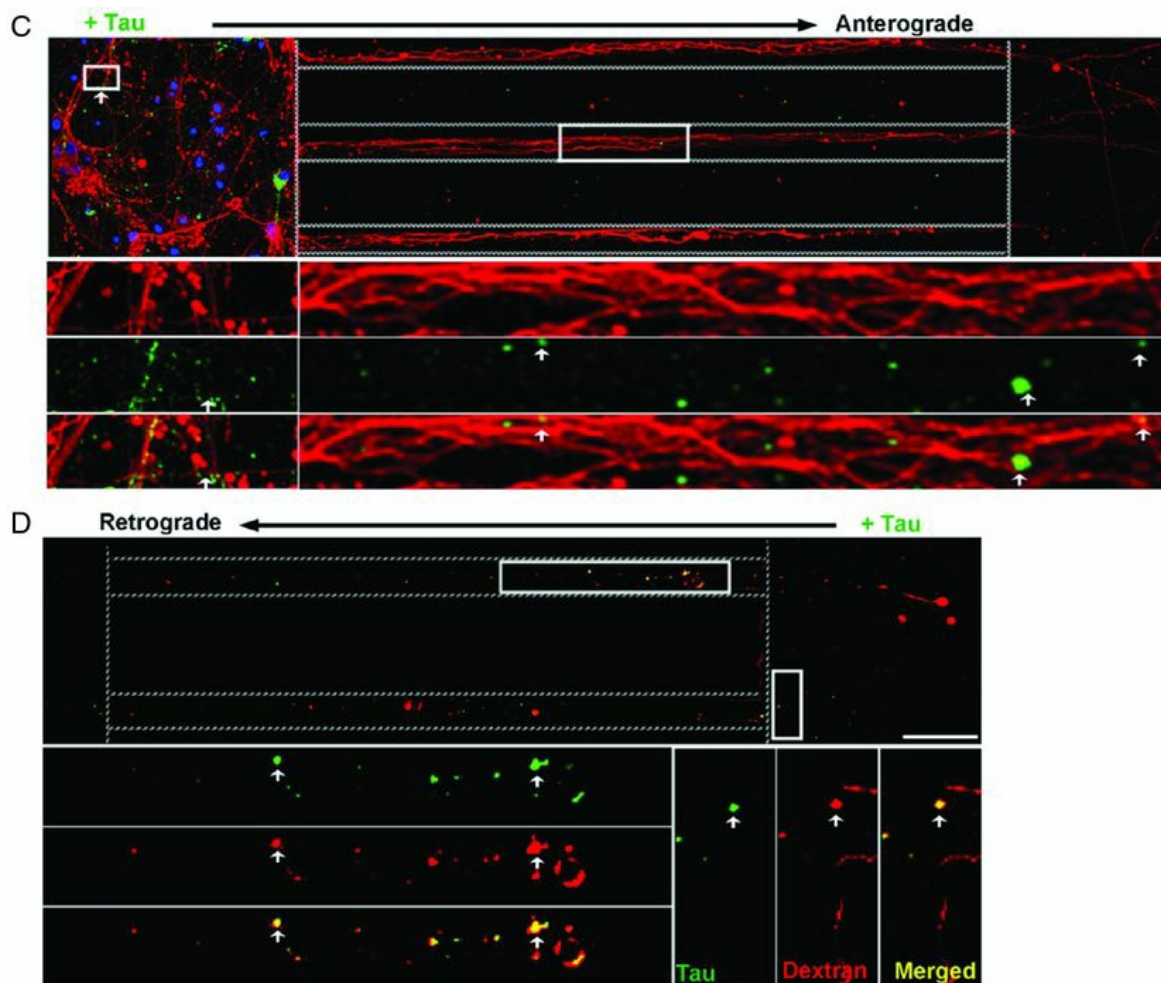


Figure 15.3 Tau can spread from neuron to neuron. (C) Microfluidic chambers with cultured neurons compartmentalized into somatodendritic (left), axon shafts (middle), and axon terminals (right). Dotted lines designate chamber separations. Neurons are stained with DAPI (blue) for nuclei and anti- β -tubulin (red) for dendrites and axons. When low-molecular-weight tau (green) is added to the somatodendritic compartment, neurons internalize tau and transport it toward the axon terminals. Also (not shown here), tau co-localizes with markers of endocytosis, dextran, and Rab5, and tau's uptake is blocked by the endocytosis inhibitor, Dynasore. (D) When tau (green) is added to the axon terminal compartment, tau undergoes endocytosis and retrograde transport down the axon shafts toward the cell bodies. Here, tau co-localizes with dextran (red), a marker of endocytosis. (C–D) Multiple insets show higher magnification of selected areas.

Reprinted with permission from Wu JW, Herman M, Liu L, *et al.* (2013).

Small misfolded Tau species are internalized via bulk endocytosis and anterogradely and retrogradely transported in neurons. *Journal of Biological Chemistry*, 288, 1856–70.

Progranulin

Mutations in *GRN* (the progranulin gene) are one of the three common autosomal dominant causes of FTD. Patients with *GRN* mutations develop FTLD-TDP (FTLD with TDP-43 proteinopathy) type A, the most common form of FTLD-TDP that is also seen in many sporadic cases [54]. Patients with *GRN* mutations also rarely present with Alzheimer's disease clinical phenotypes and amyloid deposition [55].

Pathophysiology

GRN mutations are relatively unique among genetic causes of neurodegenerative disease insofar as they are clearly loss of function, unlike many other genes where it remains unclear whether gain- or loss-of-function effects predominate. Most mutations are either nonsense or frameshift, and some deletions have also been described. These mutations thus cause haploinsufficiency of progranulin. This poses a unique therapeutic opportunity and makes it critical to identify the key progranulin functions that, when lost, cause FTD.

Progranulin is a multifunctional protein, and it is not yet clear which of its functions are most critical in regard to FTD [56]. Progranulin is a secreted glycoprotein and can be cleaved into cysteine-rich granulin peptides. Both progranulin holoprotein and the granulin peptides are biologically active and one issue that is yet to be resolved is whether the

effects of *GRN* mutations are due more to loss of progranulin or granulin activity, or a combination of both.

Progranulin has trophic effects on neurons and serves as a growth factor. Progranulin stimulates neurite outgrowth, and progranulin-deficient neurons have decreased dendritic branching [57, 58]. This function seems to be dependent on a granulin fragment [58]. Progranulin also has trophic effects on other cell types and is overexpressed in some tumors [59].

Progranulin also plays a role in inflammation. The holoprotein has mostly anti-inflammatory effects, while the granulin peptides are pro-inflammatory. It was initially reported that progranulin could compete with tumor necrosis factor- α (TNF- α) for binding to the TNF receptor [60], but others did not reproduce this result [61]. Nevertheless, progranulin knockout mice were more susceptible to inflammatory arthritis [60], and as described below show signs of neuroinflammation. Progranulin-deficient macrophages show increased phagocytosis [62] and an inflammatory profile with increased interleukin (IL)-6 and TNF- α with decreased IL-10 [63].

Finally, progranulin seems to have effects on the lysosome. Homozygous *GRN* mutations are quite rare, but were reported in one family in which two siblings with undetectable progranulin levels developed a lysosomal storage disorder, neuronal ceroid lipofuscinosis. These individuals developed a syndrome of vision loss, seizures, and cerebellar ataxia in their 20s. This disorder is thus clinically and anatomically quite different from FTD, but the observation suggests that progranulin plays a role in lysosomal function. This is also supported by the development of lipofuscin deposits in progranulin knockout mice [64–66] and genetic interactions between progranulin and the lysosomal gene, *TMEM106B* [67, 68].

Animal models

Several lines of progranulin knockout (*Grn*^{-/-}) mice have been described. They model some features of FTD, but not all. *Grn*^{-/-} mice have neuronal dysfunction with a regional proclivity resembling FTD, with the amygdala among the most affected brain regions [66]. Behaviorally, each of the different progranulin-deficient lines has some abnormalities on social tests [66, 69–71]. Most lines also have some changes in emotional behavior, such as in fear conditioning or anxiety. On the other hand, deficits in hippocampal memory develop only later in life [70, 72].

In terms of neuropathology, *Grn*^{-/-} mice do not appear to have neuron loss or TDP-43 aggregates. Insofar as these are cardinal neuropathologic features of FTD in patients with *GRN* mutations, *Grn*^{-/-} mice are an incomplete model. However, this finding also suggests that loss of progranulin is able to induce neuronal dysfunction without these features. Thus, just as tau pathology is not necessary for the dysfunction induced by tau mutations, TDP pathology is not necessary for the dysfunction induced by progranulin mutations.

Grn^{-/-} mice do have other neuropathologic abnormalities, including microgliosis and astrogliosis [63, 64, 66, 71], and formation of lipofuscin deposits [64–66]. Of course, complete progranulin deficiency in *Grn*^{-/-} mice more closely mimics the neuronal ceroid lipofuscinosis described above. Interestingly, however, these changes are not seen in heterozygous *Grn*^{+/-} mice, which model the haploinsufficiency that causes FTD. *Grn*^{+/-} mice do, though, develop behavioral deficits and amygdala dysfunction just like *Grn*^{-/-} mice [66]. Thus, the gliosis and lipofuscinosis appear not to be required for neuronal dysfunction due to progranulin haploinsufficiency.

TDP-43 and FUS

Because of several similarities between them, we will consider TDP-43 and FUS together. TDP-43 is one of the common neuropathologic substrates of FTD, including many sporadic cases as well as in patients with *C9orf72* or *GRN* mutations. TDP-43 pathology is particularly common in patients with semantic variant PPA or FTD-ALS. Mutations in the TDP-43 gene, *TARDBP*, are associated with ALS, but only rarely with pure FTD. FUS pathology is found in about 10% of FTD, making it much less common than tau or TDP-43 pathology. As with TDP-43, mutations in FUS are associated more with ALS.

Pathophysiology

TDP-43 and FUS are RNA-binding proteins with a variety of functions [73]. They are localized predominantly in the nucleus, although they can shuttle back and forth to the cytoplasm. In FTD, both proteins show cytoplasmic mislocalization and aggregation. Thus, multiple models for their toxicity are being examined, including both gain of function (due to either their abnormally high levels in the cytoplasm or toxic properties of their aggregates) and loss of function (either nuclear loss of function due to lower nuclear levels or cytoplasmic loss of function due to abnormal aggregation).

TDP-43 and FUS regulate a variety of RNA-related processes including transcription, RNA splicing, miRNA biogenesis, and translation (Figure 15.4). They are also both components of stress granules [74]. Stress granules are aggregates of RNAs and their associated binding proteins that assemble during times of stress, when it is advantageous for the cell to pause translation of non-essential mRNAs. When TDP-43 and FUS translocate from the nucleus to the cytoplasm, they normally associate with stress granules, then return to the nucleus when the stress resolves and the

stress granules dissipate. These dynamics can be disrupted by aberrant aggregation or by impaired nuclear-to-cytoplasmic trafficking of TDP-43 or FUS [74].

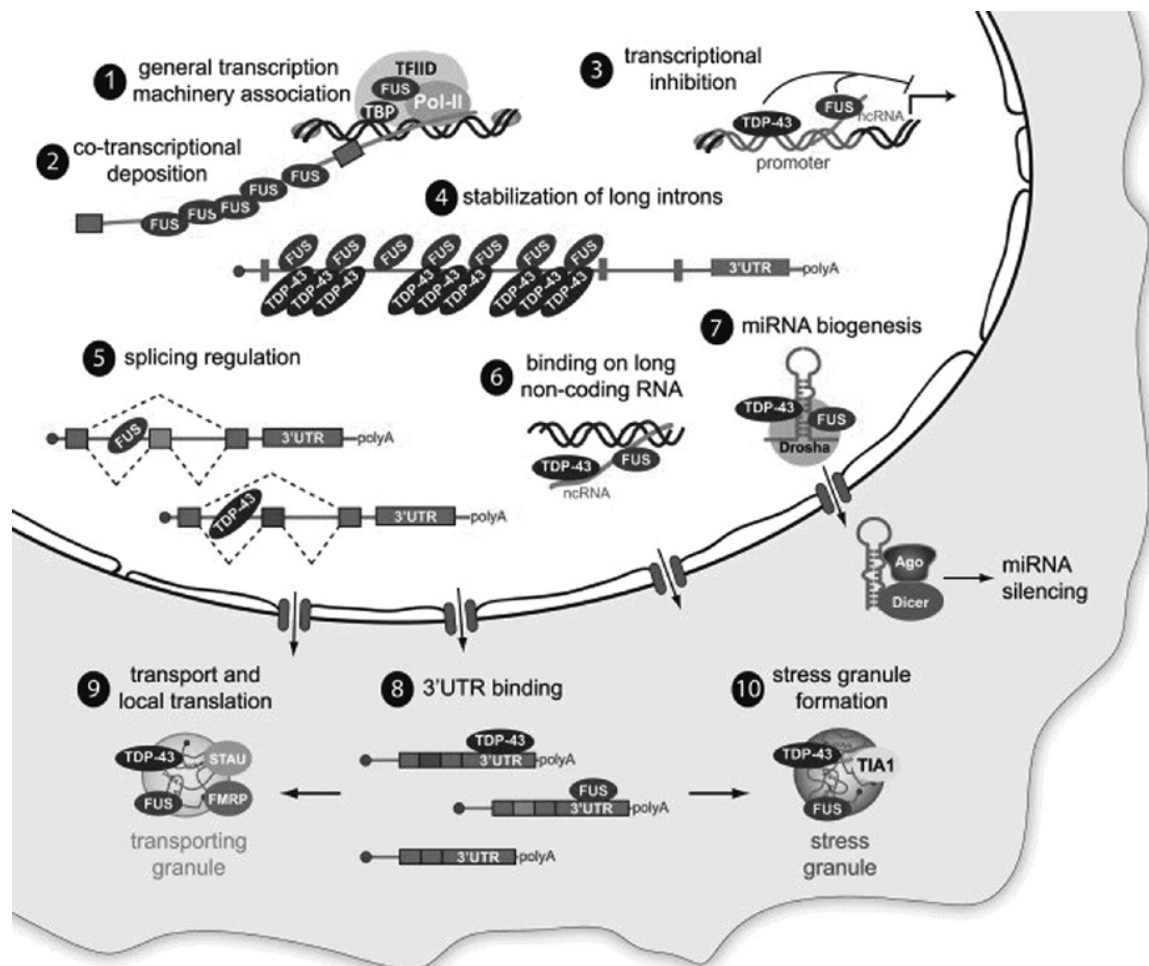


Figure 15.4 Roles for TDP-43 and FUS in RNA processing and metabolism. TDP-43 and FUS are involved in multiple steps, including regulation of transcription, RNA stabilization and splicing, miRNA biogenesis, RNA transport, and translation control.

Reprinted with permission from Ling SC, Polymenidou M, Cleveland DW (2013). Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. *Neuron*, 79, 416–38.

Mutations in TDP-43 and FUS more commonly cause ALS, but can be associated with FTD and are instructive for the mechanistic insights they

present. Mutations in both TDP-43 and FUS are concentrated in the C-terminal domain [75]. This domain in TDP-43 is important for protein aggregation and has homology to yeast prion-like domains [76]. Mutations in FUS are more distributed, but the majority (and most severe) mutations are in the C-terminus.

Both TDP-43 and FUS contain domains with homology to the yeast prions that contribute to their ability to aggregate [77]. Assembly via these domains is generally reversible and important for their ability to coalesce in stress granules, and thus for their normal physiologic function. However, this potential for prion-like aggregation also confers the potential for spreading of aggregate formation, as discussed above for tau.

Animal models

The first approach to testing for loss-of-function effects is to examine knockout mice. Homozygous *Tardbp*^{-/-} mice completely lacking TDP-43 were not viable and died at embryonic stages [78–80]. Heterozygous *Tardbp*^{+/-} mice had normal TDP-43 protein levels and so were not useful for testing loss-of-function effects [78–80]. Postnatal deletion in a conditional knockout led to death within nine days due to increased fat oxidation and resulting weight loss [81]. Most recently, motor neuron-specific conditional knockout mice were found to develop motor deficits and neuronal atrophy [82, 83], consistent with detrimental effects of loss of TDP-43 on neurons.

FUS is similarly embryonic lethal in complete knockout mice [84], but conditional knockouts have not yet been published.

TDP-43 transgenic lines have also been developed to test gain-of-function effects and have been recently reviewed [73, 85, 86]. These efforts demonstrated several salient points, including that both wild-type and

mutant TDP-43 overexpression could cause neuronal degeneration. Careful control over TDP-43 levels seems to be critical for neuronal survival, and the gene autoregulates its expression [87]. Several lines had an interesting pattern of selective vulnerability in deep cortical layers, similar to human disease [86]. Cytoplasmic aggregates do not appear critical, as several lines develop motor neuron dysfunction without cytoplasmic accumulation.

FUS transgenic mice have been difficult to generate. Somatic transgenesis using viral vectors to express FUS in the brain yielded mice with some pathologic features of human disease, including cytoplasmic inclusions of aggregated FUS [88]. A transgenic line expressing wild-type FUS develops progressive motor weakness and death within three months due to motor neuron death, with increased cytoplasmic FUS aggregates [89]. Most recently, a line expressing the R521C mutation was described [90]. These mice also die early because of motor neuron loss. Surviving motor neurons had smaller dendritic trees and evidence of DNA damage and RNA splicing defects in genes including that encoding brain-derived neurotrophic factor (*BDNF*).

VCP

Mutations in *VCP* are a rare cause of FTD, and there are several atypical features. *VCP* mutations cause a syndrome of FTD along with bone and muscle disease called inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD) [91]. Clinically, FTD in IBMPFD can be either bvFTD or semantic variant PPA [92, 93]. Neuropathologically, FTD caused by *VCP* mutations is associated with FTLD-TDP type D, a distinct subtype that is not seen in sporadic FTD or with other mutations and

characterized by TDP-43-positive neuronal intranuclear inclusions and dystrophic neurites with few neuronal cytoplasmic inclusions [94].

Pathophysiology

VCP (called p97 in mouse) is a member of the ATPase associated with diverse cellular activities (AAA⁺) family. Like other AAA⁺ proteins, VCP/p97 has numerous functions, including regulating protein degradation through the ubiquitin proteasome system, endoplasmic reticulum-associated degradation, and autophagy. The protein uses its ATPase domain to unfold or refold ubiquitinated proteins and disassemble protein complexes. Disease-associated mutations in VCP are concentrated in a conserved region of the folded protein, and a single mutation, R155C, is responsible in most families. This region of the protein is responsible for recognizing substrates.

Animal models

Complete loss of VCP/p97 is embryonic lethal [95]. Many transgenic lines have been developed, although some are focused on expression in muscle or bone to understand those pathologies of IBMPFD. Both transgenic and knock-in line models of *VCP*-related FTD have been developed, generally expressing either the R155H or A232E mutations.

These models exhibit a range of age-dependent muscle, bone, and brain disease related to human IBMPFD. In general, these mice develop various pathologies in brain, bone, and muscle related to IBMPFD. They develop TDP-43 positive inclusions [96–98]. Spinal motor neurons are lost and denervation develops in late age [99]. A recent study found that some deficits in these mice can be rescued with a lipid-enriched diet [100].

CHMP2B

CHMP2B mutations are the least common autosomal dominant cause of FTD, occurring in only a few families [18]. Patients present with a fairly typical clinical syndrome of behavioral variant FTD [101], but neuropathologically have FTLD-UPS, an uncommon pathology in which there are ubiquitinated neuronal cytoplasmic inclusions that do not contain tau, TDP-43, or FUS [102, 103]. More recently, missense mutations have been identified that cause FTD and/or motor neuron disease, and these cases do appear to have TDP-43 pathology [104].

Pathophysiology

CHMP2B is involved in trafficking proteins to the lysosome as part of the endosomal sorting complex required for transport III (ESCRT-III). FTD-associated mutations in *CHMP2B* affect alternative splicing of the last exon and lead to generation of two novel transcripts with alternative C-termini, CHMP2B^{Intron5} and CHMP2B^{Δ10} [105]. CHMP2B^{Intron5} fails to dissociate normally from the ESCRT-III complex, impairing its function and leading to accumulation of autophagosomes [106].

Animal models

Both knockout and transgenic models of CHMP2B have been developed [107]. Deficits are seen in transgenic mice expressing CHMP2B^{Intron5}, but not in knockout mice, suggesting a gain-of-function effect due to the aberrant protein. CHMP2B^{Intron5} mice develop a progressive axonopathy with inclusions of ubiquitinated proteins that are negative for TDP-43 and FUS, as in the FTLD-UPS pathology in patients with CHMP2B mutations [107].

Conclusions

The pathophysiology of FTD appears to be just as complex and heterogeneous as its clinical syndromes and neuropathologic bases. Is there a unified mechanism or final common pathway to FTD? The answer to this question is not yet clear, but there are some common themes. One of the clearest is dysfunction of RNA processing proteins, as C9ORF72, TDP-43, and FUS all have effects on various aspects of RNA processing [108]. Another possible theme is impairment of protein handling, in which both VCP and CHMP2B are involved.

FTD has begun, in the last decade, to let slip some of its secrets. Given the identification of so many of the key players and the development of interesting models, this trend is sure to continue.

References

1. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;**72**:245–56.
2. Renton AE, Majounie E, Waite A, *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;**72**:257–68.
3. Rutherford NJ, Heckman MG, DeJesus-Hernandez M, *et al.* Length of normal alleles of *C9ORF72* GGGGCC repeat do not influence disease phenotype. *Neurobiol Aging* 2012;**33**:2950.e5–7.
4. Ciura S, Lattante S, Le Ber I, *et al.* Loss of function of *C9orf72* causes motor deficits in a zebrafish model of amyotrophic lateral sclerosis. *Ann Neurol* 2013;**74**(2):180–7.

-
5. Xi Z, Zinman L, Moreno D, *et al.* Hypermethylation of the CpG island near the G4C2 repeat in ALS with a *C9orf72* expansion. *Am J Hum Genet* 2013;**92**: 981–9.
-
6. Belzil VV, Bauer PO, Prudencio M, *et al.* Reduced *C9orf72* gene expression in c9FTD/ALS is caused by histone trimethylation, an epigenetic event detectable in blood. *Acta Neuropathol* 2013;**126**:895–905.
-
7. Haeusler AR, Donnelly CJ, Periz G, *et al.* *C9orf72* nucleotide repeat structures initiate molecular cascades of disease. *Nature* 2014;**507**:195–200.
-
8. Xu Z, Poidevin M, Li X, *et al.* Expanded GGGGCC repeat RNA associated with amyotrophic lateral sclerosis and frontotemporal dementia causes neurodegeneration. *Proc Natl Acad Sci USA* 2013;**110**:7778–83.
-
9. Gendron TF, Bieniek KF, Zhang YJ, *et al.* Antisense transcripts of the expanded *C9ORF72* hexanucleotide repeat form nuclear RNA foci and undergo repeat-associated non-ATG translation in c9FTD/ALS. *Acta Neuropathol* 2013;**126**:829–44.
-
10. Ash PE, Bieniek KF, Gendron TF, *et al.* Unconventional translation of *C9ORF72* GGGGCC expansion generates insoluble polypeptides specific to c9FTD/ALS. *Neuron* 2013;**77**:639–46.
-
11. Mori K, Weng SM, Arzberger T, *et al.* The *C9orf72* GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTLD/ALS. *Science* 2013;**339**:1335–8.
-
12. Lagier-Tourenne C, Baughn M, Rigo F, *et al.* Targeted degradation of sense and antisense *C9orf72* RNA foci as therapy for ALS and frontotemporal degeneration. *Proc Natl Acad Sci USA* 2013;**110**:E4530–9.
-
13. Lee YB, Chen HJ, Peres JN, *et al.* Hexanucleotide repeats in ALS/FTD form length-dependent RNA foci, sequester RNA binding proteins, and are

neurotoxic. *Cell Rep* 2013;**5**:1178–86.

14. van Swieten J, Spillantini MG. Hereditary frontotemporal dementia caused by tau gene mutations. *Brain Pathol* 2007;**17**:63–73.

15. Hutton M, Lendon CL, Rizzu P, *et al.* Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998;**393**:702–5.

16. Poorkaj P, Bird TD, Wijsman E, *et al.* Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol* 1998;**43**:815–25.

17. Spillantini MG, Murrell JR, Goedert M, *et al.* Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci USA* 1998;**95**:7737–41.

18. Alzheimer Disease & Frontotemporal Dementia Mutation Database. Available from: <http://www.molgen.ua.ac.be/FTDMutations>.

19. Alonso Adel C, Mederlyova A, Novak M, *et al.* Promotion of hyperphosphorylation by frontotemporal dementia tau mutations. *J Biol Chem* 2004;**279**:34873–81.

20. Liu F, Gong CX. Tau exon 10 alternative splicing and tauopathies. *Mol Neurodegener* 2008;**3**:8.

21. Goedert M, Jakes R. Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization. *EMBO J* 1990;**9**:4225–30.

22. Brion JP, Tremp G, Octave JN. Transgenic expression of the shortest human tau affects its compartmentalization and its phosphorylation as in the pretangle stage of Alzheimer's disease. *Am J Pathol* 1999;**154**:255–70.

23. Gotz J, Probst A, Spillantini MG, *et al.* Somatodendritic localization and

hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform. *EMBO J* 1995;**14**:1304–13.

24. Probst A, Gotz J, Wiederhold KH, *et al.* Axonopathy and amyotrophy in mice transgenic for human four-repeat tau protein. *Acta Neuropathol* 2000;**99**:469–81.

25. Ishihara T, Hong M, Zhang B, *et al.* Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform. *Neuron* 1999;**24**:751–62.

26. Ishihara T, Zhang B, Higuchi M, *et al.* Age-dependent induction of congophilic neurofibrillary tau inclusions in tau transgenic mice. *Am J Pathol* 2001;**158**: 555–62.

27. Higuchi M, Ishihara T, Zhang B, *et al.* Transgenic mouse model of tauopathies with glial pathology and nervous system degeneration. *Neuron* 2002;**35**: 433–46.

28. Lewis J, McGowan E, Rockwood J, *et al.* Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. *Nat Genet* 2000;**25**:402–5.

29. Götz J, Chen F, Barmettler R, *et al.* Tau filament formation in transgenic mice expressing P301L tau. *J Biol Chem* 2001;**276**:529–34.

30. SantaCruz K, Lewis J, Spires T, *et al.* Tau suppression in a neurodegenerative mouse model improves memory function. *Science* 2005;**309**:476–81.

31. Allen B, Ingram E, Takao M, *et al.* Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein. *J Neurosci* 2002;**22**:9340–51.

32. Spires TL, Orne JD, SantaCruz K, *et al.* Region-specific dissociation of

neuronal loss and neurofibrillary pathology in a mouse model of tauopathy. *Am J Pathol* 2006;**168**:1598–607.

33. de Calignon A, Fox LM, Pitstick R, *et al.* Caspase activation precedes and leads to tangles. *Nature* 2010;**464**:1201–4.

34. Andorfer C, Acker CM, Kress Y, *et al.* Cell-cycle reentry and cell death in transgenic mice expressing nonmutant human tau isoforms. *J Neurosci* 2005;**25**:5446–54.

35. Mocanu MM, Nissen A, Eckermann K, *et al.* The potential for β -structure in the repeat domain of tau protein determines aggregation, synaptic decay, neuronal loss, and coassembly with endogenous tau in inducible mouse models of tauopathy. *J Neurosci* 2008;**28**:737–48.

36. Kuchibhotla KV, Wegmann S, Kopeikina KJ, *et al.* Neurofibrillary tangle-bearing neurons are functionally integrated in cortical circuits in vivo. *Proc Natl Acad Sci USA* 2014;**111**:510–14.

37. Rocher AB, Crimins JL, Amatrudo JM, *et al.* Structural and functional changes in tau mutant mice neurons are not linked to the presence of NFTs. *Exp Neurol* 2010;**223**:385–93.

38. Yoshiyama Y, Higuchi M, Zhang B, *et al.* Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron* 2007;**53**:337–51.

39. Sydow A, Van der Jeugd A, Zheng F, *et al.* Tau-induced defects in synaptic plasticity, learning, and memory are reversible in transgenic mice after switching off the toxic tau mutant. *J Neurosci* 2011;**31**:2511–25.

40. Hoover BR, Reed MN, Su J, *et al.* Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. *Neuron* 2010;**68**:1067–81.

-
- 41.** Yamada K, Holth JK, Liao F, *et al.* Neuronal activity regulates extracellular tau in vivo. *J Exp Med* 2014;**211**:387–93.
-
- 42.** Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. *J Biol Chem* 2009;**284**:12845–52.
-
- 43.** Kfoury N, Holmes BB, Jiang H, *et al.* Trans-cellular propagation of tau aggregation by fibrillar species. *J Biol Chem* 2012;**287**:19440–51.
-
- 44.** Guo JL, Lee VM. Seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles. *J Biol Chem* 2011;**286**:15317–31.
-
- 45.** Wu JW, Herman M, Liu L, *et al.* Small misfolded tau species are internalized via bulk endocytosis and anterogradely and retrogradely transported in neurons. *J Biol Chem* 2013;**288**:1856–70.
-
- 46.** Clavaguera F, Bolmont T, Crowther RA, *et al.* Transmission and spreading of tauopathy in transgenic mouse brain. *Nat Cell Biol* 2009;**11**:909–13.
-
- 47.** Liu L, Drouet V, Wu JW, *et al.* Trans-synaptic spread of tau pathology in vivo. *PLoS One* 2012;**7**:e31302.
-
- 48.** de Calignon A, Polydoro M, Suárez-Calvet M, *et al.* Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron* 2012;**73**:685–97.
-
- 49.** Seeley WW, Crawford RK, Zhou J, *et al.* Neurodegenerative diseases target large-scale human brain networks. *Neuron* 2009;**62**:42–52.
-
- 50.** Seeley WW. Anterior insula degeneration in frontotemporal dementia. *Brain Struct Funct* 2010;**214**:465–75.
-
- 51.** Rabinovici GD, Seeley WW, Kim EJ, *et al.* Distinct MRI atrophy patterns in autopsy-proven Alzheimer's disease and frontotemporal lobar degeneration. *Am J Alzheimers Dis Other Demen* 2007;**22**:474–88.

52. Zhou J, Greicius MD, Gennatas ED, *et al.* Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain* 2010;**133**:1352–67.

53. Zhou J, Gennatas ED, Kramer JH, *et al.* Predicting regional neurodegeneration from the healthy brain functional connectome. *Neuron* 2012;**73**:1216–27.

54. Mackenzie IR, Neumann M, Baborie A, *et al.* A harmonized classification system for FTLT-TDP pathology. *Acta Neuropathol* 2011;**122**:111–13.

55. Perry DC, Lehmann M, Yokoyama JS, *et al.* Progranulin mutations as risk factors for Alzheimer disease. *JAMA Neurol* 2013;**70**:774–8.

56. Cenik B, Sephton CF, Kutluk Cenik B, *et al.* Progranulin: a proteolytically processed protein at the crossroads of inflammation and neurodegeneration. *J Biol Chem* 2012;**287**:32298–306.

57. Van Damme P, Van Hoecke A, Lambrechts D, *et al.* Progranulin functions as a neurotrophic factor to regulate neurite outgrowth and enhance neuronal survival. *J Cell Biol* 2008;**181**:37–41.

58. Gass J, Lee WC, Cook C, *et al.* Progranulin regulates neuronal outgrowth independent of sortilin. *Mol Neurodegener* 2012;**7**:33.

59. Bateman A, Bennett HP. The granulin gene family: from cancer to dementia. *Bioessays* 2009;**31**:1245–54.

60. Tang W, Lu Y, Tian QY, *et al.* The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. *Science* 2011;**332**:478–84.

61. Chen X, Chang J, Deng Q, *et al.* Progranulin does not bind tumor necrosis factor (TNF) receptors and is not a direct regulator of TNF-dependent signaling

or bioactivity in immune or neuronal cells. *J Neurosci* 2013;**33**:9202–13.

62. Kao AW, Eisenhut RJ, Martens LH, *et al.* A neurodegenerative disease mutation that accelerates the clearance of apoptotic cells. *Proc Natl Acad Sci USA* 2011;**108**:4441–6.

63. Yin F, Banerjee R, Thomas B, *et al.* Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. *J Exp Med* 2010;**207**:117–28.

64. Ahmed Z, Sheng H, Xu YF, *et al.* Accelerated lipofuscinosis and ubiquitination in granulin knockout mice suggest a role for progranulin in successful aging. *Am J Pathol* 2010;**177**:311–24.

65. Petkau TL, Neal SJ, Milnerwood A, *et al.* Synaptic dysfunction in progranulin-deficient mice. *Neurobiol Dis* 2012;**45**:711–22.

66. Filiano AJ, Martens LH, Young AH, *et al.* Dissociation of frontotemporal dementia-related deficits and neuroinflammation in progranulin haploinsufficient mice. *J Neurosci* 2013;**33**:5352–61.

67. Finch N, Carrasquillo MM, Baker M, *et al.* *TMEM106B* regulates progranulin levels and the penetrance of FTLD in *GRN* mutation carriers. *Neurology* 2011;**76**:467–74.

68. Chen-Plotkin AS, Unger TL, Gallagher MD, *et al.* *TMEM106B*, the risk gene for frontotemporal dementia, is regulated by the microRNA-132/212 cluster and affects progranulin pathways. *J Neurosci* 2012;**32**:11213–27.

69. Kayasuga Y, Chiba S, Suzuki M, *et al.* Alteration of behavioural phenotype in mice by targeted disruption of the progranulin gene. *Behav Brain Res* 2007;**185**:110–18.

70. Yin F, Dumont M, Banerjee R, *et al.* Behavioral deficits and progressive neuropathology in progranulin-deficient mice: a mouse model of frontotemporal

dementia. *FASEB J* 2010;**24**:4639–47.

71. Ghoshal N, Dearborn JT, Wozniak DF, *et al.* Core features of frontotemporal dementia recapitulated in progranulin knockout mice. *Neurobiol Dis* 2012;**45**:395–408.

72. Wils H, Kleinberger G, Pereson S, *et al.* Cellular ageing, increased mortality and FTLD-TDP-associated neuropathology in progranulin knockout mice. *J Pathol* 2012;**228**:67–76.

73. Ling SC, Polymenidou M, Cleveland DW. Converging mechanisms in ALS and FTD: disrupted RNA and protein homeostasis. *Neuron* 2013;**79**:416–38.

74. Li YR, King OD, Shorter J, *et al.* Stress granules as crucibles of ALS pathogenesis. *J Cell Biol* 2013;**201**:361–72.

75. Lattante S, Rouleau GA, Kabashi E. *TARDBP* and *FUS* mutations associated with amyotrophic lateral sclerosis: summary and update. *Hum Mutat* 2013;**34**:812–26.

76. Cushman M, Johnson BS, King OD, *et al.* Prion-like disorders: blurring the divide between transmissibility and infectivity. *J Cell Sci* 2010;**123**:1191–201.

77. King OD, Gitler AD, Shorter J. The tip of the iceberg: RNA-binding proteins with prion-like domains in neurodegenerative disease. *Brain Res* 2012;**1462**:61–80.

78. Wu LS, Cheng WC, Hou SC, *et al.* TDP-43, a neuro-pathosignature factor, is essential for early mouse embryogenesis. *Genesis* 2010;**48**:56–62.

79. Sephton CF, Good SK, Atkin S, *et al.* TDP-43 is a developmentally regulated protein essential for early embryonic development. *J Biol Chem* 2010;**285**:6826–34.

80. Kraemer BC, Schuck T, Wheeler JM, *et al.* Loss of murine TDP-43 disrupts

motor function and plays an essential role in embryogenesis. *Acta Neuropathol* 2010;**119**:409–19.

81. Chiang P-M, Ling J, Jeong YH, *et al.* Deletion of TDP-43 down-regulates *Tbc1d1*, a gene linked to obesity, and alters body fat metabolism. *Proc Natl Acad Sci USA* 2010;**107**:16320–4.

82. Iguchi Y, Katsuno M, Niwa J, *et al.* Loss of TDP-43 causes age-dependent progressive motor neuron degeneration. *Brain* 2013;**136**:1371–82.

83. Wu LS, Cheng WC, Shen CK. Targeted depletion of TDP-43 expression in the spinal cord motor neurons leads to the development of amyotrophic lateral sclerosis-like phenotypes in mice. *J Biol Chem* 2012;**287**:27335–44.

84. Hicks GG, Singh N, Nashabi A, *et al.* *Fus* deficiency in mice results in defective B-lymphocyte development and activation, high levels of chromosomal instability and perinatal death. *Nat Genet* 2000;**24**:175–9.

85. Tsao W, Jeong YH, Lin S, *et al.* Rodent models of TDP-43: recent advances. *Brain Res* 2012;**1462**:26–39.

86. Roberson ED. Mouse models of frontotemporal dementia. *Ann Neurol* 2012;**72**:837–49.

87. Ayala YM, De Conti L, Avendano-Vazquez SE, *et al.* TDP-43 regulates its mRNA levels through a negative feedback loop. *EMBO J* 2011;**30**:277–88.

88. Verbeeck C, Deng Q, DeJesus-Hernandez M, *et al.* Expression of *Fused in sarcoma* mutations in mice recapitulates the neuropathology of FUS proteinopathies and provides insight into disease pathogenesis. *Mol Neurodegener* 2012;**7**:53.

89. Mitchell JC, McGoldrick P, Vance C, *et al.* Overexpression of human wild-type FUS causes progressive motor neuron degeneration in an age- and dose-dependent fashion. *Acta Neuropathol* 2013;**125**:273–88.

90. Qiu H, Lee S, Shang Y, *et al.* ALS-associated mutation FUS-R521C causes DNA damage and RNA splicing defects. *J Clin Invest* 2014;**124**:981–99.

91. Watts GD, Wymer J, Kovach MJ, *et al.* Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat Genet* 2004;**36**:377–81.

92. van der Zee J, Pirici D, Van Langenhove T, *et al.* Clinical heterogeneity in 3 unrelated families linked to VCP p.Arg159His. *Neurology* 2009;**73**:626–32.

93. Kim EJ, Park YE, Kim DS, *et al.* Inclusion body myopathy with Paget disease of bone and frontotemporal dementia linked to VCP p.Arg155Cys in a Korean family. *Arch Neurol* 2011;**68**:787–96.

94. Forman MS, Mackenzie IR, Cairns NJ, *et al.* Novel ubiquitin neuropathology in frontotemporal dementia with valosin-containing protein gene mutations. *J Neuropathol Exp Neurol* 2006;**65**:571–81.

95. Müller JM, Deinhardt K, Rosewell I, *et al.* Targeted deletion of p97 (VCP/CDC48) in mouse results in early embryonic lethality. *Biochem Biophys Res Commun* 2007;**354**:459–65.

96. Badadani M, Nalbandian A, Watts GD, *et al.* VCP associated inclusion body myopathy and Paget disease of bone knock-in mouse model exhibits tissue pathology typical of human disease. *PLoS One* 2010;**5**:e13183.

97. Custer SK, Neumann M, Lu H, *et al.* Transgenic mice expressing mutant forms VCP/p97 recapitulate the full spectrum of IBMPFD including degeneration in muscle, brain and bone. *Hum Mol Genet* 2010;**19**:1741–55.

98. Rodriguez-Ortiz CJ, Hoshino H, Cheng D, *et al.* Neuronal-specific overexpression of a mutant valosin-containing protein associated with IBMPFD promotes aberrant ubiquitin and TDP-43 accumulation and cognitive dysfunction in transgenic mice. *Am J Pathol* 2013;**183**:504–15.

99. Yin HZ, Nalbandian A, Hsu CI, *et al.* Slow development of ALS-like spinal cord pathology in mutant valosin-containing protein gene knock-in mice. *Cell Death Dis* 2012;**3**:e374.

100. Llewellyn KJ, Nalbandian A, Jung KM, *et al.* Lipid-enriched diet rescues lethality and slows down progression in a murine model of VCP-associated disease. *Hum Mol Genet* 2014;**23**:1333–44.

101. Gydesen S, Brown JM, Brun A, *et al.* Chromosome 3 linked frontotemporal dementia (FTD-3). *Neurology* 2002;**59**:1585–94.

102. Holm IE, Englund E, Mackenzie IR, *et al.* A reassessment of the neuropathology of frontotemporal dementia linked to chromosome 3. *J Neuropathol Exp Neurol* 2007;**66**:884–91.

103. Holm IE, Isaacs AM, Mackenzie IR. Absence of FUS-immunoreactive pathology in frontotemporal dementia linked to chromosome 3 (FTD-3) caused by mutation in the *CHMP2B* gene. *Acta Neuropathol* 2009;**118**:719–20.

104. Cox LE, Ferraiuolo L, Goodall EF, *et al.* Mutations in *CHMP2B* in lower motor neuron predominant amyotrophic lateral sclerosis (ALS). *PLoS One* 2010;**5**:e9872.

105. Skibinski G, Parkinson NJ, Brown JM, *et al.* Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat Genet* 2005;**37**:806–8.

106. Lee JA, Beigneux A, Ahmad ST, *et al.* ESCRT-III dysfunction causes autophagosome accumulation and neurodegeneration. *Curr Biol* 2007;**17**:1561–7.

107. Ghazi-Noori S, Froud KE, Mizielinska S, *et al.* Progressive neuronal inclusion formation and axonal degeneration in *CHMP2B* mutant transgenic mice. *Brain* 2012;**135**:819–32.

108. Thomas M, Alegre-Abarrategui J, Wade-Martins R. RNA dysfunction and aggregate pathology at the centre of an amyotrophic lateral sclerosis/frontotemporal dementia disease continuum. *Brain* 2013;**136**:1345–60.

Section 5



Treatment

Chapter 16

Functional disability and the impact of frontotemporal dementia in everyday life



Claire M. O'Connor and Eneida Mioshi

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

In which stage is she in?

I think my husband can still drive safely...

Can he stay alone at home while I go to work?

While these are very common questions that we face after delivering an accurate diagnosis of frontotemporal dementia (FTD), until quite recently we could only rely on clinical experience or anecdotal evidence to answer them. Studies investigating functional disability and clinical disease staging in FTD are relatively new, and while many everyday questions remain unanswered, we now have a growing body of literature that specifically addresses these important management issues. In this chapter we will describe the different patterns of functional disability in the three main variants of FTD (including a brief section on atypical parkinsonian

syndromes), their patterns of disease progression from a functional perspective, and the relationship (or lack of) between functional disability and cognitive and behavioral symptoms.

This chapter draws on the current published literature on functional disability in FTD, and also on our own experience evaluating and advising patients and carers in the past 10 years. Over these years, we have set up a successful routine of functional assessment via carer interviews with Professor John Hodges' group, initially in Cambridge, UK, and then in Sydney, Australia within the Frontier Research Group. We have also conducted numerous performance-based assessments at the homes of FTD patients (various subtypes of the Picks complex, including progressive supranuclear palsy [PSP], corticobasal degeneration [CBD], as well as motor neuron disease [MND]). By applying systematic assessment of everyday living impairment in FTD, both cross-sectional and longitudinally, we have set out to investigate the interactions between cognitive deficits, behavioral changes, family carers, and functional disability. This process has also led to better understanding of disease progression, culminating in novel measures of disease severity and progression specifically designed for FTD, and the application of novel non-pharmacologic interventions for patients and carers within research settings, currently underway.

This chapter will also provide dementia management strategies for carers and professionals in overcoming day-to-day difficulties. Finally, a brief section demonstrating the major impact of functional deficits on those around the patient, including their spouses and children, will also be included.

How activities of daily living are defined and evaluated

The term activity of daily living (ADL) refers to activities of varying levels of complexity which are carried out daily and are key for an individual's independent community living [1]. ADLs are generally subclassified into basic and instrumental activities ([Figure 16.1](#)). Basic activities, or basic ADLs, relate to day-to-day core survival abilities such as eating, washing, walking, dressing, transferring from bed to wheelchair, and going to the toilet. Instrumental activities of daily living (instrumental ADLs), by contrast, are defined by their higher level of complexity, and reflect the ability to live independently in the community. They encompass use of the telephone, managing finances, medications, going out, meal preparation, household chores, and leisure activities [2, 3].

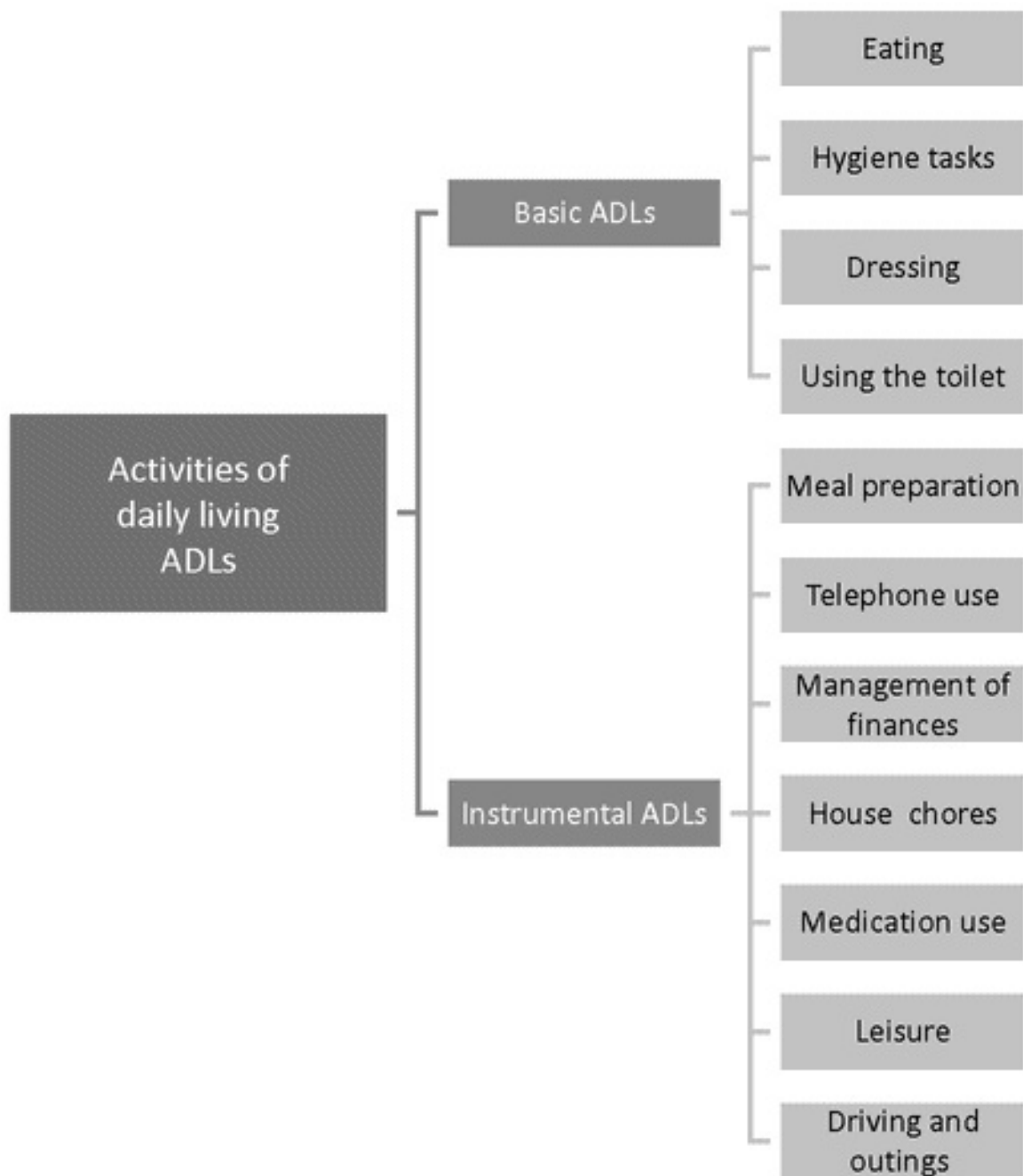


Figure 16.1 Schematic diagram showing activities of daily living (ADLs) subclassified into basic (Basic ADLs) and instrumental (Instrumental ADLs).

The assessment of functional abilities should be included in clinical investigations of any individual with FTD, as they can aid in determining dementia severity and prognosis. The picture of ADL impairment in FTD tends to be quite complex because of the interplay of cognitive and behavioral deficits and their distinct impact on functional abilities.

Importantly, assessment of ADLs should extend to include the primary progressive aphasia (PPAs), where most of the focus at diagnosis remains on assessment of language function, with little attention to assessment of functional performance [4, 5].

The assessment of functional decline can be conducted in a variety of ways. Informant-based report (questionnaire or interview) are commonly used in dementia settings. In research settings, performance-based assessments of ADL function offer a more controlled analysis of the performance. However, performance-based assessments can be rather constraining because they require specialist training and can be more time-consuming.

A point of debate in dementia, when assessing ADLs, is that scales generally overstate house chores, with a risk of gender bias. In addition, cultural bias can also be present, especially in countries where domestic workers such as cleaners or gardeners have a prominent role in the household. To reduce bias, one needs to take this contextual information into consideration when interpreting scores in the face of cognitive decline and/or behavioral change – and comparison to premorbid level of functioning is paramount (Figure 16.2). As such, ADL scales tend to not offer normative tables as seen in neuropsychological tests, because each individual should be compared to themselves. When assessing functional abilities we are examining change in the individual's ability to perform their usual tasks, and from this standpoint, assessment of functional decline can offer a sensitive measure of change from premorbid functioning.



Figure 16.2 Competence in house chores can be culturally specific, and ADL assessments should be interpreted individually and with premorbid levels in mind. “Anunciacao” (Annunciation), by Luciana Comenote and Coletivo C.U.P.I.N.S (Central Unida de Pessoas Inventando Novas Saidas), 2011. Technique: Woodcut on Fabric.

Reproduced with permission from the artist.

www.facebook.com/coletivocupins

Our experience in working in functional disability has led us to develop a functional and behavioral staging tool, which was developed particularly for FTD patients. By utilizing a data-driven approach (Rasch analysis), we were able to develop and validate a tool that could stage accurately FTD patients from a clinical perspective. Importantly, by relying on functional abilities and behavioral symptoms, the scale is not bound to floor effects seen on cognitive tests due to language deficits. The Frontotemporal Dementia Behavioral Rating Scale (FTDFRS) [6] is based on an interview to the proxy (most of the time a primary carer who is also a family member) and takes about 15–20 minutes to complete, depending on the severity of the patient. The FTDFRS can classify patients in six different stages: very mild; mild; moderate; severe; very severe; profound.

The FTDFRS [6] has demonstrated ability to differentiate between the three main FTD variants (Figure 16.3), where behavioural variant FTD (bvFTD) patients are much more severe than PPA patients when matched for length of symptoms. We have also demonstrated that the bvFTD patients reach the severe stages of dementia in about 5 years, while it can take up to 10 years for semantic variant PPA (svPPA) patients to reach the same level of dementia severity. Importantly, if comparing the FTDFRS with the original Clinical Dementia Rating Scale (CDR) [7], our scale demonstrates greater sensitivity to patients' impairment and level of dependency to carers or environment (Figure 16.4). Finally, the FTDFRS is also more sensitive to functional deficits in Alzheimer's disease (AD) [8] than the original CDR.

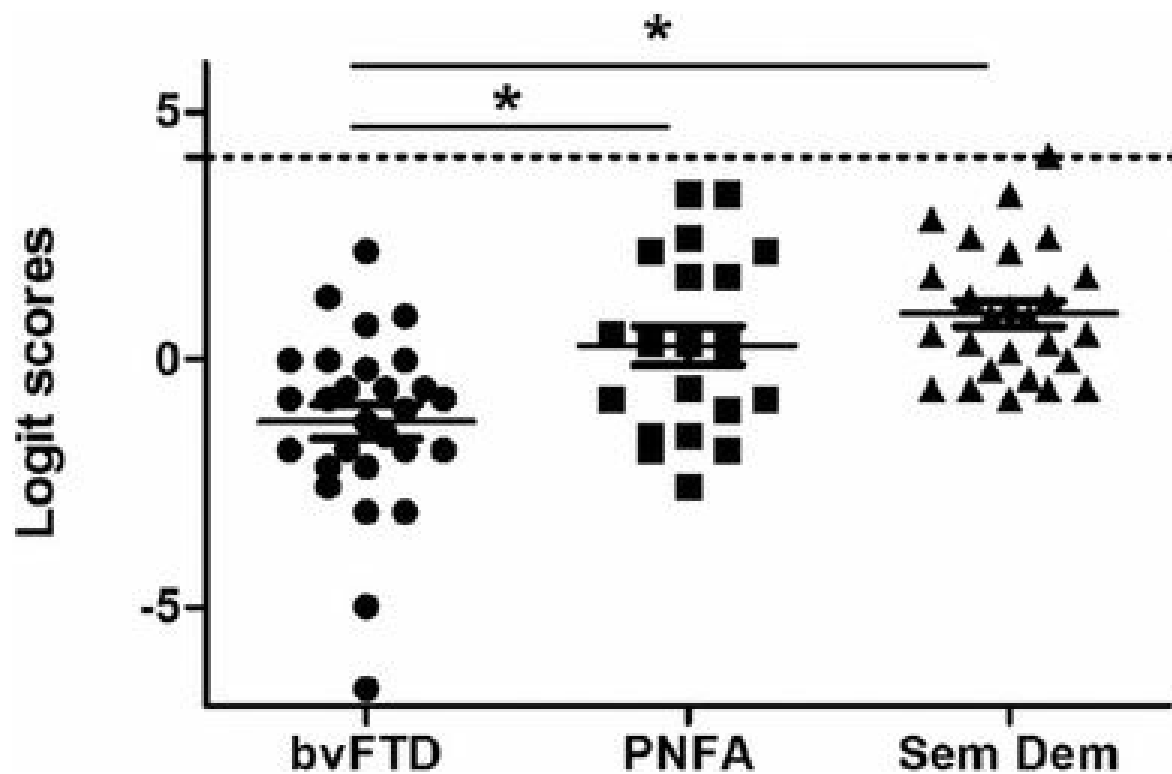


Figure 16.3 Profiles of disease severity in behavioural variant FTD (bvFTD), non-fluent PPA (PNFA), and semantic variant PPA (Sem Dem) patients. *From:* Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR (2010). Clinical staging and disease progression in frontotemporal dementia. *Neurology*, 74(20), 1591–7.

Reproduced with permission from Wolters Kluwer Health.

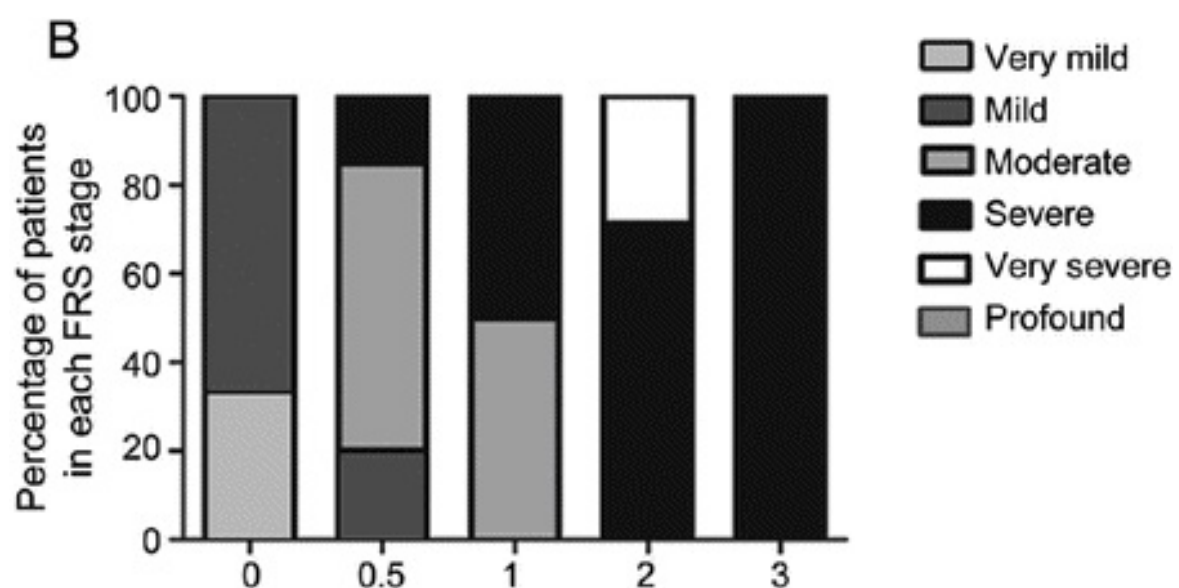


Figure 16.4 Proportion of FTD patients in each FRS severity category

according to the Clinical Dementia Rating Scale ratings. *From: Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR (2010). Clinical staging and disease progression in frontotemporal dementia. Neurology, 74(20), 1591–7.*

Reproduced with permission from Wolters Kluwer Health.

Importantly, the FTDFRS is not the only option in staging patients in FTD. The Mayo group has also addressed this gap by extending the CDR for FTD, which resulted in the CDR-FTLD [9]. The CDR-FTLD includes two additional domains, language and comportment, and has been shown to have greater sensitivity for detecting changes in FTD than the original CDR, with great applicability for future drug trials.

Patterns of functional impairment in FTD subtypes, and their progression

The underlying neural changes that lead to distinct initial symptoms in bvFTD and the PPAs, also lead to various patterns of functional disability. These impairments also progress in different degrees depending on the FTD variant (Figure 16.5). This section will present profiles of functional impairment by FTD subtype, and will also include a brief section on logopenic variant PPA, CBD, and PSP.

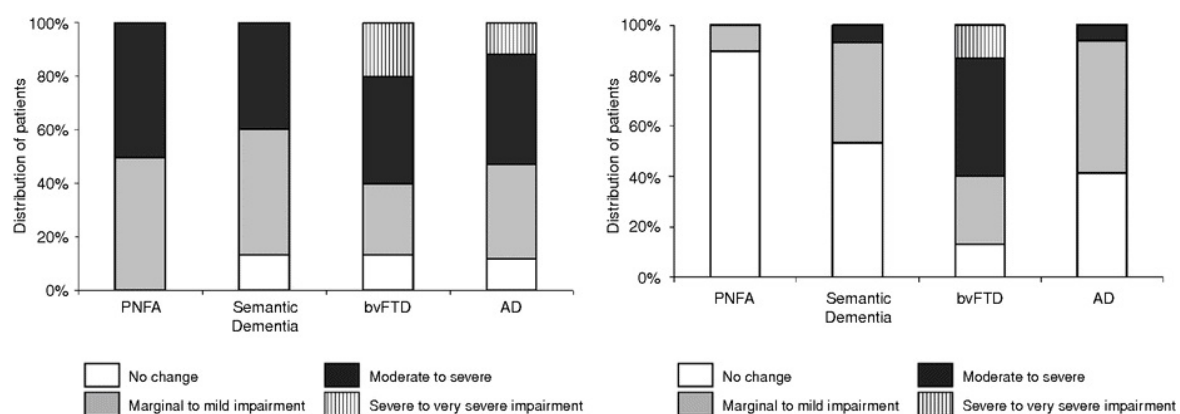


Figure 16.5 Percentage of FTD and AD patients presenting with different

degrees of impairment on basic ADLs and instrumental ADLs. *From*: Mioshi E, Kipps CM, Dawson K, Mitchell J, Graham A, Hodges JR (2007). Activities of daily living in frontotemporal dementia and Alzheimer disease. *Neurology*, 68(24), 2077–84.

Reproduced with permission from Wolters Kluwer Health.

Behavioral variant FTD

Impairment in executive functioning and ADL performance occurs early in the disease for patients with bvFTD [10]. We have shown [11, 12] a similar level of impairment in basic ADL and instrumental ADLs in bvFTD, but this finding is not universal [13]. This discrepancy is likely to be due to different methodologic approaches in instrument selection or inclusion of patients at different stages of the dementia. In general dementia, ADL decline follows a well-known pattern, in which instrumental ADLs are usually affected first, followed by late deficits in basic ADLs. However, this is usually not the case for bvFTD, where both instrumental complex tasks as well as basic ADLs are affected from disease onset. The great majority of bvFTD patients (90%) are impaired in basic ADL performance [11]. As such, impairment on basic ADLs features in the diagnostic criteria for FTD [14, 15].

In comparison with other FTD variants, bvFTD patients perform more poorly in both instrumental ADLs and basic ADLs than svPPA and non-fluent variant PPA (nfvPPA) patients in most activities, including household chores, shopping, finances, leisure, and self-care [11, 13, 16]. In comparison with AD, bvFTD patients show similar levels of instrumental ADL impairment, but more severe basic ADL impairment than AD patients when matched for length of symptoms. The rate of progression of functional disability is also marked in bvFTD, where patients decline more rapidly than other variants over a 12-month period [6, 12, 17, 18].

Assessment of functional decline in bvFTD is not only important because of its severity from the early stages, but also because it is not directly associated with cognitive deficits. In other words, high scores on standard cognitive tests, such as the Addenbrooke's Cognitive Examination or the Mini-Mental State Examination (MMSE) can lead to an erroneous assumption that the patient is not very impaired at home or in the community. It has been demonstrated that bvFTD patients may continue to score relatively well on cognitive assessments when in reality there is marked worsening in the patient's abilities to perform activities at home and in the community safely [19]. (Patients with PPA variants show a clear decline on these tests from an early stage, and this will be discussed below.) When the striking impairment to perform ADLs is added to a low or absent level of insight into their own changes, patients can become evidently vulnerable to scams and malicious behavior, but can also present risk to others around if not monitored closely.

Driving is usually one of the most distressing areas to address with patients and families. In most cases, speeding and risk-taking behavior have been suggested as being related to behaviors such as disinhibition and agitation [20, 21]. Arranging for a professional driving assessment allows for an objective assessment from an external party, and minimizes the chances of the patient blaming the loss of the license on the spouse or family. However, the removal of the driver's license may not impact on their attempts to drive. Common issues with shopping are related to overspending, purchasing unnecessary items such as those shown on television commercials, paper advertisements, or even via door-to-door sellers at home – as a result of poor judgment and impulsivity [22]. In some extreme cases, patients might shoplift, which can be very distressing to the family. It is often reported that while the patient is able to go to the shops independently, they might ignore the shopping list, only returning with items

which interest them (such as biscuits, lollies, or other favorite items). Impaired judgment can lead to mistakes in financial management, but the patient might be rigid about retaining their role as financial manager, refusing help, and in some cases hiding correspondences and bills received in the mail. bvFTD patients can become very prone to email scams, and many families have lost considerable amounts of money as a result of these behaviors. Inappropriate phone calls such as calling people or services multiple times a day, and disclosing credit card or personal details to telemarketers can occur quite often [22]. Changes in behavior may lead to over-medicating, or refusal to take medication [23, 24], which can become stressful scenarios for the family. Apathy and executive dysfunction are common symptoms that may impact on a person's participation in meal preparation [24–26]. An important aspect to management of any of these behaviors is carer education about FTD and how the condition manifests in behaviors. [Table 16.1](#) offers a number of strategies that might be useful in managing instrumental ADLs in bvFTD.

Table 16.1 Management strategies for instrumental ADLs in bvFTD

Instrumental ADLs			
bvFTD			
Driving	<ul style="list-style-type: none"> ✓ Hide car keys ✓ Disable the car and tell the person you are waiting on a mechanic ✓ Sell the person's car and tell them it was stolen or is at the repair shop ✓ Store the car out 	Shopping	<ul style="list-style-type: none"> ✓ Provide the person with a limited shopping list with fewer items ✓ Notify local shops of the person's condition and propensity to shop lift and make arrangements to

of sight to reduce
visual reminders
[\[22\]](#)

return/pay for items
✓ Cancel or
remove the person's
credit card
✓ Provide the
person with a
weekly allowance
✓ Organize for
someone to
accompany patient
to the shops

**Finance and
correspondence**

✓ Redirect mail to
a PO Box, family
member, or a
neighbor's house
✓ Change
passwords to online
accounts to prevent
any serious
incidents of financial
mismanagement [\[22\]](#)
✓ Email scams:
check patient's email
account to monitor
potential
engagement with
scammers

Telephone

✓ Unplug home
phone when carer is
out to prevent
unwanted
telemarketing calls
✓ Contact
telephone company
to block
telemarketing calls
✓ Redirect calls to
house to the carer's
mobile phone
✓ Set up a PIN for
outgoing calls – the
telephone company
can help

Medications

✓ If multiple
medications are
required, use of a
Webster-pack or
Dosette box may
assist with
administration of
correct
prescriptions
✓ Liaise with the

Housework

✓ Set up an
activity for a
person, and assist
them to begin the
task (sometimes
apathy may
primarily impact on
a person's ability to
initiate a task)
✓ Carer education

	<p>pharmacist about alternative forms of administration, such as adding liquid or powdered forms to food</p> <p>✓ Carers might need to manage the person's medications from an early stage</p>		<p>around amending expectations about how much the person should participate or be engaged in an activity [22]</p>
Meal preparation	<p><u>Apathy</u></p> <p>✓ Set up the activity for the person, and assist them to begin the task, for example, place out a chopping board, knife, and carrot, then demonstrate by cutting first slice</p> <p>✓ If apathy is a more pervasive symptom, an important strategy may be around carer education, so they may amend their own expectations about how much the person can participate or be engaged in an activity [22]</p>	Meal preparation (cont.)	<p><u>Executive dysfunction</u></p> <p>✓ Planning impairments may be addressed by providing a recipe “written” with step-by-step pictures, or by breaking the task down into more manageable steps, such as peeling the carrots or chopping the potatoes [70]. Providing aspects of an activity that a person <i>can do</i> allows them to remain actively involved in ADLs [67]</p>

Basic ADLs are also affected in bvFTD from an early stage, contrary to most dementias, where there is usually a clear gradient of loss from the most complex to the simplest tasks.

Neglect in personal hygiene is an early symptom, and can affect routines with showering, brushing teeth, and grooming (e.g., shaving, combing hair, and using makeup). This neglect worsens as the disease progresses [12, 24]. Patients often wear a reduced selection of outfits, or tend to repeat a favorite piece (e.g., shirt, dress, underwear), which can lead to refusal to change even when washing is obviously needed. Also, wearing inappropriate clothing can be a consequence of several deficits: inability to choose appropriate outfits for a specific occasion, inability to recognize weather conditions or even potentially changes in temperature regulation. Incontinence can occur quite early in the disease and can be the result of behaviors such as apathy, decreased insight, or even disinhibition, rather than a specific physiologic cause. Examples include passing urine sitting on the couch rather than getting up; passing urine while eating cake as the patient did not want to leave the table; using pot plants and rubbish bins as urinals in the care facility. Of note, it is important to consider that incontinence can also result from health conditions such as prostate enlargement or urinary tract infections, and therefore these should be ruled out as potential causes with the patient's doctor. Eating habits are generally affected from an early stage, with changes in food preference being very common in bvFTD, in particular increased preference for sweet foods and carbohydrates [24, 27–29], which can lead to marked weight increase. In most cases, patients tend to seek out preferred foods, rummaging through the refrigerator and pantry, or even going shopping recurrently to obtain the item. [Table 16.2](#) shows strategies that might be helpful in managing basic ADLs in bvFTD patients.

Table 16.2 Management strategies for basic ADLs in bvFTD

Basic ADLs			
bvFTD			
Hygiene	<ul style="list-style-type: none"> ✓ Prompting and reminding become a key requirement of carers in these situations ✓ Carers are often required to re-evaluate their own expectations of how frequently the person needs to shower or shave ✓ Some carers have successfully used sweets or chocolates as rewards for hygiene activities 	Continence	<ul style="list-style-type: none"> ✓ Set up a toileting routine where patients use the toilet at regular intervals throughout the day and before bedtime ✓ If patient urinates in inappropriate places, place signs on these places directing the person to use the toilet
Dressing	<ul style="list-style-type: none"> ✓ Remove dirty clothes while the person is in the shower, and provide a clean, similar outfit ready to be donned when they get out. Some carers even purchase multiple copies of a favored shirt so it may be easily transferred for washing ✓ Where possible, carers should consider ignoring the clothes choice, i.e., if the patient is just at home, or if it's a cool day and they 	Eating	<ul style="list-style-type: none"> ✓ Keeping food out of sight might be enough to deter overeating caused by utilization behavior [15, 23] ✓ Install a

are not at risk of overheating
✓ If it is really necessary for certain clothes to be worn for an occasion, provide an appropriate outfit ready for the person when they finish in the shower, while ensuring all other clothes are out of sight

lock on the fridge and/or pantry to prevent unwanted rummaging if the behavior has escalated
[\[22\]](#)

✓ Placing healthy snacks such as fruit or nuts visibly on the kitchen bench or table may catch the person's attention before they reach the pantry or fridge

Primary progressive aphasia: semantic variant

Impairments in semantic memory and difficulty recognizing faces, voices, or names are common in svPPA and impact on the person's ability to engage in instrumental ADLs such as social events, using the telephone, and appropriately managing correspondence [\[11\]](#). These impairments can ultimately result in early retirement if the person was in the workforce at diagnosis.

Patients with svPPA show similar rates of impairment to bvFTD and nfvPPA in instrumental ADLs; however, they differ in their performance of basic ADLs [11]. Patients with svPPA usually have preservation of basic ADLs for a number of years compared with instrumental ADLs, which are usually impaired from an early stage.

In terms of functional progression over time, svPPA patients have been reported to decline at a less rapid rate than both nfvPPA and bvFTD patients [8, 30, 31]. This is also seen when measuring dementia stages: svPPA patients are quite stable in disease progression for many years, from a functional perspective [6, 31].

On cognitive tests, patients with svPPA are often globally impaired owing to their language deficits; however, at home they often maintain their engagement in routine tasks until later into disease progression. This is likely to be associated with the rigid routines that are extremely common in patients with svPPA; future studies should address this potential relationship.

Ability to perform instrumental ADLs in svPPA is therefore well maintained for years, despite the evident semantic deficits and rigid behavior. Driving skills are often well preserved until the moderate stage. Impairments in language can pose a risk for these patients if they were to be involved in a car accident or altercation where they may have difficulty communicating with authorities. Ability to shop independently remains for some years if the patient is purchasing habitual items. Semantic impairments may eventually create difficulty with recognizing products and produce. Overspending is not a common issue in svPPA; patients in fact may become increasingly frugal with money, which often manifests as obsessive searching for “bargains.” Managing medications is also usually not a problem for svPPA patients for a number of years, which seems to be made possible by their ritualized routines. Meal preparation can be affected by

deficits in semantic knowledge of kitchen implements and foods [32], and ability to perform household chores is often retained until the late stages of the dementia, often driven by compulsions such as the daily need to pack the dishwasher in a certain way [33]. Social outings tend to be greatly affected by changes in behavior, especially disinhibition. These behaviors may include (but are not limited to): approaching people or children they do not know when out in public, commenting loudly about the way people look, or providing bizarre demonstrations such as dancing or singing [34]. When disinhibition is pronounced, carers can become very embarrassed and may prefer to limit outings (see Case 2). Overall, patients with svPPA adhere to rigid, time-constrained routines, which in fact seem to facilitate their engagement in a limited range of activities [33, 35]. Narrowing of interests is another common symptom seen in svPPA patients, where they may develop a more focused, obsessive interest in only one or two activities – and will spend a large amount of time engaging within these [36], e.g., spending hours per day engaged with jigsaw puzzles [37]. Case 3 provides an example of a carer changing her own reaction to a situation, rather than trying to change the patient's behavior. Attempting to interrupt a person's rigid routine is likely to elicit distress, irritability, and aggression [36]. [Table 16.3](#) contains a number of strategies that might be useful in managing instrumental ADLs in svPPA and nvPPA.

Table 16.3 Management strategies for instrumental ADLs in svPPA and nvPPA

Instrumental ADLs			
svPPA and nvPPA			
Driving	✓ Carry an official letter from the patient's doctor or	Shopping	✓ Include visual elements on a shopping list, e.g., cut the label from

information card in the person's wallet explaining their situation, and providing contact details of their carer, family members, or close friends

- ✓ Have the person wear a medical alert necklace or bracelet containing the patient's address and emergency contact numbers [68]

products at home which need replacing

- ✓ Carer education with a focus on coping strategies and thought modification to manage their own reactions to a behavior of little consequence, e.g., catalogue “bargain” hunting

Finance and correspondence

- ✓ When possible, support patients to maintain their involvement with previously held roles such as managing the finances to help them to retain a sense of independence and control
- ✓ Close family or friends may provide assistance through proofreading documents prior to the person

Housework

- ✓ Supporting patient may extend level of engagement in roles involving housework and garden [31]
- ✓ Relax the standard of performance to allow continued participation in activities, even if the person does the chore incorrectly. For example, someone may wash dishes in cold water with no detergent. In this

sending them

case, the carer may ignore the mistakes, or may want to wash again when the person is not in the room. Either way, the patient has been allowed to continue contributing to household tasks

Telephone

- ✓ Preparing a script before making a phone call may provide some guidance, and instill some confidence
- ✓ Some patients with nfvPPA prefer to write emails or text messages rather than making phone calls as writing allows more time for the person to generate their message, while also providing spelling and grammatical software assistance
- ✓ Receiving written correspondence

Meal preparation

- Semantic impairment
 - ✓ Picture-based instructions using images of ingredients, implements, and the process steps may address semantic impairments [32]
- Apraxia
 - ✓ Task breakdown may be useful in this situation; they may be able to peel vegetables, or assist by stirring. Monitor use of appliances and sharp or heavy items in the kitchen. Assist person where necessary (e.g., carrying

may be equally as beneficial to allow the person time to interpret the written message, rather than trying to quickly process spoken words without the visual cues provided by speaking with someone in person

heavy pots, or using knives), while allowing the person to continue with tasks they remain able to complete

Leisure and outings

Disinhibition

- ✓ Carry little information cards to hand out to people explaining that their family member has a brain condition which causes behavioral changes
- ✓ Avoid public places, such as supermarkets, at peak times to reduce the possibility of any public demonstrations
- ✓ While at the supermarket, ensure the patient has a role such as pushing the trolley

Leisure and outings (cont.)

Communication impairments

- ✓ Planning ahead by only attending events with fewer people, and only planning to stay for a limited time may help with reducing chances of the person becoming overwhelmed and of social withdrawal
- ✓ Informing friends and family of the person's condition prior to an event may help to generate a supportive environment, while also providing opportunity to

to keep them engaged

- ✓ Visit restaurants earlier, or call ahead to request a table in a quiet part of the restaurant to reduce the possibility for triggering the patient's desire to demonstrate their “skills” to people, such as their lunge-walk

- ✓ If at the park with grandchildren, take a favorite snack or game which could be used as a distraction for the patient if other children arrive [22]

Rigidity

- ✓ Working within the rigid routines of a person, rather than trying to cease them, is likely to generate a more positive outcome for both the person and the carer

impart some useful communication strategies

- ✓ Use of communication cards or boards, gestures, or language-based technologies tailored to specific social situations may support a person with PPA to participate [68]

- ✓ Avoid talking over the person

- ✓ Offer assistance with word-finding after allowing reasonable time for them to express the word themselves

- ✓ Allow more time to communicate

- ✓ Ensure you speak clearly, at an appropriate pace, tone, and volume

- ✓ Couple verbal communication with body language such as gestures, eye contact, and facial expressions

- ✓ Limit distractions such as ambient music or crowds

✓ Communicating in statements rather than questions can support a person to be involved in a conversation without feeling pressured to verbally contribute themselves

Ability to perform basic ADLs is well maintained in svPPA until the very late stages of dementia, even though patients might not be able to name products or to verbally communicate the activities they are intending to perform. Late in the disease, difficulties in differentiating products appear, e.g., patients can mistake shaving cream for toothpaste. As with all dementias, patients might refuse to perform personal hygiene tasks at the severe stages and excessive prompting often leads to increased stress and unsuccessful outcomes. Dressing issues might also appear later in the dementia. Changes in food preferences are also common in svPPA: restrictive dieting or rigidity with specific foods are common [25, 36], which can be accompanied by fixed times to set the table and eat. Secondary to their semantic deficits, patients may also consume unsafe items such as raw meat, mouldy food, or non-food items such as soap or a kitchen sponge in the severe stages of the dementia [38]. Strategies that might be helpful in managing basic ADLs in svPPA and nfvPPA are shown in Table 16.4.

Table 16.4 Management strategies for basic ADLs in svPPA and nfvPPA

Basic ADLs			
svPPA and nfvPPA			
Hygiene	✓ Remove any non-essential	Dressing	✓ Remove dirty

items from the bathroom

- ✓ Store items specific to one hygiene task, such as toothbrush and toothpaste, together in a clear, marked container. Labeling the container with a photo of the person doing that task will illustrate the contents and their correct use

- ✓ Confusion often occurs with varied packaging on products; ensure consistency in the replacement of any product, for example the same brand, size, and color of shampoo [71]

- ✓ Health professionals can assist a carer to modify their expectations about the person's personal hygiene and to generate an appropriate care plan to match the person's needs while limiting carer burden from unnecessary prompting and confrontations

clothes while the person is in the shower, and provide a clean, similar outfit ready to be donned when they get out. Some carers even purchase multiple copies of a favored shirt so it may be easily transferred for washing

- ✓ Where possible, carers should consider ignoring the clothes choice, i.e., if the patient is just at home, or if it's a cool day and they are not at risk of overheating

- ✓ If it is really necessary for certain clothes to be worn for an occasion, provide an appropriate outfit ready for the person when they finish in the shower, while ensuring all other clothes are out of

sight

Continence	✓ Continence strategies used in general dementia such as continence wear and the toileting schedules mentioned for bvFTD would be useful in these situations	Eating	✓ Ensure food in the fridge is monitored according to expiry dates, and that foods such as raw meats are made inaccessible to the person [22]
-------------------	--	---------------	---

Primary progressive aphasia: non-fluent variant

Frank language dysfunction in nfvPPA leads to impairments in writing and reading and eventually mutism, with great impact on the ability of patients to participate in leisure activities such as social events and other interpersonal interactions [35]. The majority of patients with nfvPPA do not show any changes in their performance on basic ADLs for a number of years post-diagnosis, despite performing poorly on general cognitive assessments [13, 39, 40]. While patients with nfvPPA have relatively preserved basic ADLs, impairments in instrumental ADLs are common, ranging from mild to severe impairment by around two years into disease progression [39, 41].

Longitudinal changes to function over a 12-month period have recently been suggested to be more marked in nfvPPA than in svPPA [6]. In nfvPPA, clear associations between global cognition and functional disability have been demonstrated [39, 40], especially in cohorts of patients assessed longitudinally.

Instrumental ADLs are impaired from an early stage also in nfvPPA, though mostly secondary to language deficits. Driving skills are often preserved until late in the disease, unless apraxia appears. As with svPPA, impairments in language can become a risk for these patients if they were to

be involved in a car accident where they may have difficulty communicating with others. Patients with nvPPA may be able to continue managing financial tasks for a relatively long period into the disease. Telephone use tends to become an issue as patients avoid it, because of awareness of their communication limitations; many patients prefer to text or email, even if spelling mistakes are obvious. It is not exactly clear why nvPPA patients reduce their participation in meal preparation, since they often maintain good semantic knowledge of kitchen-related items. It is likely that a combination of early apraxia and deficits in multitasking can hinder their ability to prepare meals [42]. The ability to perform household chores is often retained until late into the dementia, when other combined cognitive deficits impact on their ability to perform chores. Insight into their language deficits is a common cause of social withdrawal.

Basic ADLs are very well preserved for a large numbers of years in nvPPA. However, once the patient reaches the severe stages, refusal to engage in personal hygiene tasks can occur as in most dementias. Incontinence does not usually appear until very late into disease progression, and can therefore be managed according to standard dementia practices. Eating and dietary changes are rarely seen in nvPPA.

Primary progressive aphasia: logopenic variant

Patients with logopenic variant progressive aphasia (lvPPA) have a distinctive pattern of language disturbance, and have only recently been identified as an independent subgroup [43]. There is an association between lvPPA and AD pathology rather than FTD pathology [44–46]. It is important to consider that most studies investigating nvPPA prior to this delineation would probably contain patients with both FTD and AD pathology. lvPPA patients seem to decline twice as fast on cognitive tests than svPPA patients,

with patients becoming globally impaired after a 12-month follow-up period. Cognitive deficits in svPPA patients tend to remain relatively isolated to language domains [47, 48].

Considering this recent delineation of PPA variants, it is not surprising that only one study investigating the impact of lvPPA on ADLs [39] has been found. lvPPA patients seem to present with similar ADL abilities when compared with patients with nvfPPA or AD (Figure 16.6). Interestingly, the range of disability is much greater in lvPPA than in nvfPPA, suggesting that nvfPPA patients have more localized dysfunction than lvPPA. This is in line with the underlying AD pathology observed in lvPPA. Additionally, it is possible that the marked changes in language confer an early diagnosis of dementia, when ADLs are only mildly affected and memory issues are not prominent.

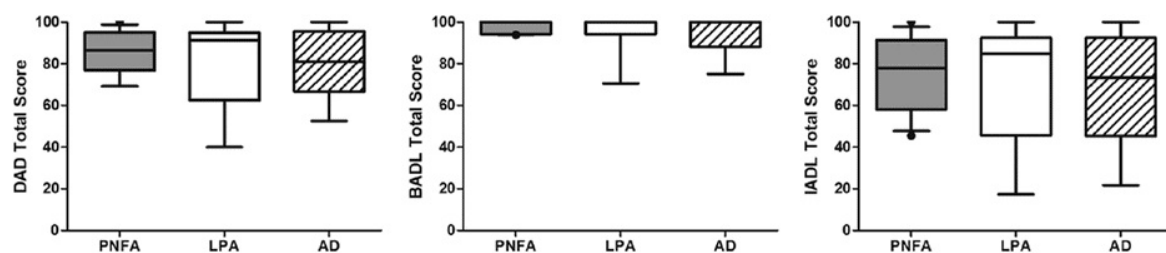


Figure 16.6 Distribution of ADL scores by dementia subgroups: nvfPPA (PNFA), lvPPA (LPA), and Alzheimer's disease (AD). *From: Jang J, Cushing N, Clemson L, Hodges JR, Mioshi E (2012). Activities of daily living in progressive non-fluent aphasia, logopenic progressive aphasia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 33(5), 354–60.*

Reproduced with permission from Karger.

In terms of longitudinal decline, lvPPA patients seem to follow the more common pattern of decline of dementias in general (including AD and nvfPPA), where instrumental ADL deficits appear earlier than basic ADL

impairment [39]. More studies are needed to elucidate differences and similarities in patterns of functional decline in lvPPA and other PPAs.

Corticobasal degeneration and progressive supranuclear palsy

CBD and PSP are syndromes from the Pick's disease spectrum, and can overlap considerably with nvPPA for a number of years [42, 49]. CBD and PSP patients present with marked functional disability across instrumental and basic ADLs from an early stage [40], with CBD patients presenting with worse impairments than PSP patients when matched for length of symptoms. The few studies published to date have focused on the disability secondary to apraxia [50–52] in CBD, or detailed case studies in PSP [53]. In fact, we have demonstrated that memory deficits are more relevant to functional disability than apraxia in CBD and PSP.

Despite the great overlap between CBD and PSP, and the main variants of FTD [49], only one study to date has compared the impact of these dementia subtypes on functional disability. In terms of general cognitive decline, CBD, PSP, and nvPPA patients might score similarly [40] but patterns of functional disability, on the other hand, seem to differ between these subgroups (Figure 16.7). Patients with CBD are more impaired than both PSP and nvPPA patients in ADL functioning when matched for length of symptoms. Additional studies are required to understand the interactions of cognitive, motor, and behavioral deficits in these syndromes.

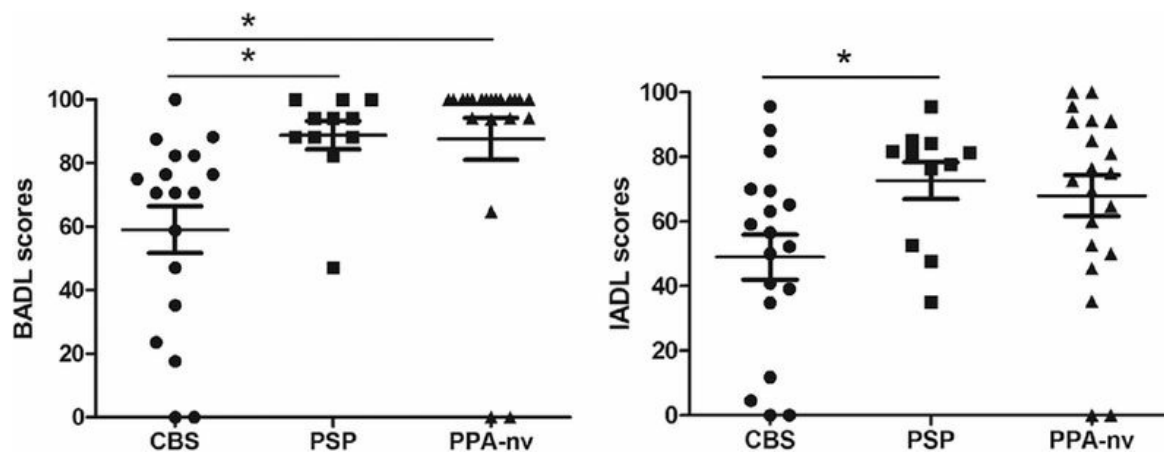


Figure 16.7 Group differences in basic ADLs and instrumental ADLs for CBS, PSP, and nvPPA (PPA-nv) patients. *From: Cushing N, Jang J, O'Connor CM, et al. (2013). Disability in atypical parkinsonian syndromes is more dependent on memory dysfunction than motor symptoms.*

Parkinsonism & Related Disorders, 19(4), 436–40.

Reproduced with permission from Karger.

Relationship between cognitive deficits and behavioral changes with ADLs

The interactions of behavioral symptoms and cognitive deficits, and their impact on functional disability in FTD depend on each variant, and have not been extensively investigated to date.

Simultaneous changes to cognitive function and behavioral manifestations occur in the mild stages of bvFTD, which are often accompanied by marked changes in ADL performance [54, 55]. Executive deficits common in bvFTD can lead to serious impairments in planning, which can impact on daily function in ADLs [56]. More rapid functional decline in bvFTD has been associated with poor performance in language, visuospatial, and executive outcomes [55]. Significant correlations between MMSE and functional scores for patients with bvFTD have been reported

[57], but despite this evidence there is no consensus to date that cognitive deficits are the main factors behind marked functional disability in bvFTD [11]. It seems that the relationship between functional and cognitive scores in bvFTD patients is clearer in longitudinal studies [12], or could be highly dependent on measures used. The role of apathy on functional disability in bvFTD, on the other hand, seems better defined and more relevant than executive deficits [24].

Interestingly, in svPPA no correlation between general cognitive tests (such as the MMSE) and functional scores seems to exist [13]. This is likely to be explained by the bias towards language abilities in general cognitive testing, where svPPA patients tend to appear more impaired than they actually are at home. For nvPPA, a more clear association between general cognitive testing and functional disability has been described [39, 40].

Broadly speaking, localized regions of brain atrophy have been associated with scores in ADLs in FTD (all variants combined) [58], which have largely differed from areas associated with functional decline in AD. In FTD, the main areas implicated with functional disability (instrumental ADLs) were the prefrontal areas, including dorsolateral prefrontal cortex, orbitofrontal cortex and frontal pole, thalamus, cingulate, hippocampus, and amygdala (Figure 16.8). For AD patients, atrophic areas associated with instrumental ADL deficits were more widespread and included temporal, parietal, frontal, and caudate regions. A converging region for instrumental ADL impairment across FTD and AD seems to be the superior left prefrontal cortex, which not surprisingly is deemed responsible for executive abilities. With regard to basic ADLs, specific regions were also identified for FTD and AD. In FTD, atrophic areas in the prefrontal cortex, cingulate regions were implicated in functional disability. In AD patients a more widespread atrophy picture emerged once again, with other additional areas (besides the temporal lobes and cingulate) associated with basic ADL

scores, including hippocampus, caudate, parts of the frontal lobes, and parietal regions. Interestingly, no common region associated with basic ADLs and both FTD and AD were found, suggesting that different symptomatology leads to ADL dysfunction in these dementias.

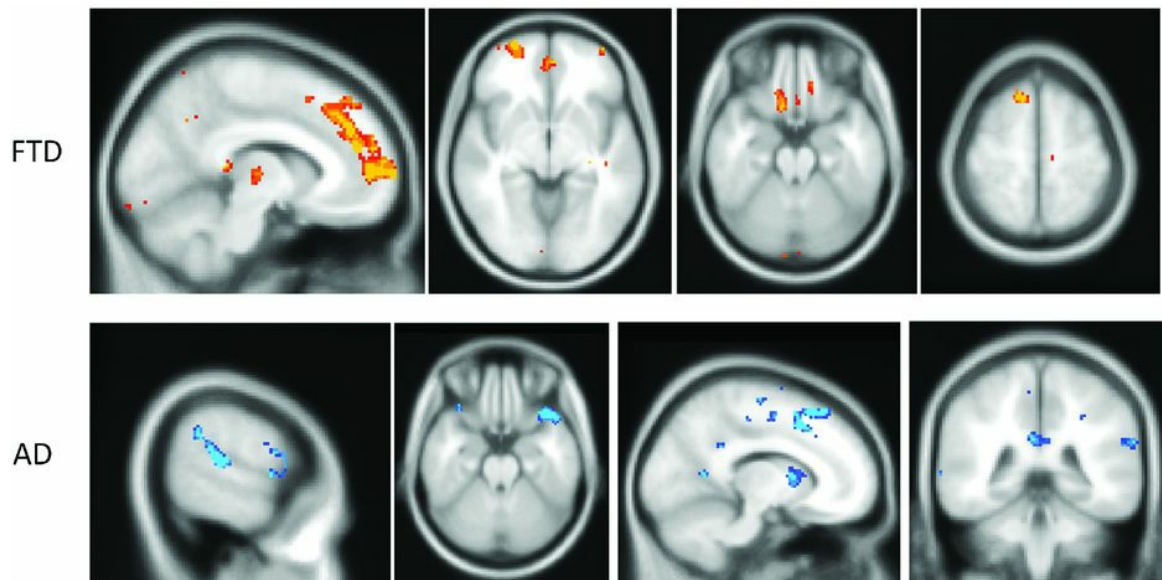


Figure 16.8 VBM analyses showing different brain areas that correlate with activities of daily living in FTD and AD. *From: Mioshi E, Hodges JR, Hornberger M (2013). Neural correlates of activities of daily living in frontotemporal dementia. *Journal of Geriatric Psychiatry and Neurology*, 26(1), 51–7.*

Reproduced with permission from SAGE Publications.

These differences highlight the importance of a clear understanding of dementia subtype and prognosis from an early stage, given that functional disability and disease progression will follow different patterns in these subtypes, requiring tailored interventions for more efficacious results.

Impact of functional disability and disease progression on family carers

An area of more recent interest of investigation in FTD is carer burden and stress. Given the marked changes in personality, social interaction, as well as language deficits, it is not surprising that family members involved with FTD patients present with high rates of burden and stress [61]. FTD has some unique attributes which should be considered when investigating the impact on carers. The early onset of disease may have financial implications if the person is still working, or if the carer also needs to stop work in order to take on a caring role. This change of roles from spouse to carer at an earlier life stage, while in some cases dependent children are still living at home [59], can understandably lead to great levels of burden.

In fact, carer burden in FTD is much greater than in AD [60, 61] and controls [62]. Carer burden is a complex construct, with disease-related factors (such as symptoms), carer-related factors (such as depressive symptoms), as well as physical environmental factors (such as residential care) interacting and coming into play. Behavioral changes appear to be correlated with carer distress and burden in FTD [63], but this is likely to be due to methodologic approaches where both burden and symptoms are measured in one single assessment. For instance, carers of svPPA patients tend not to report as high levels of burden as bvFTD carers, even though svPPA and bvFTD patients present with very similar behavioral changes, e.g., rigidity and disinhibition. It is likely that disease progression is a much stronger factor in carer burden in FTD [64], as shown in [Figure 16.9](#). Carer-related factors such as mood and social network are also implicated in carer burden [64]. Finally, it is not clear whether nursing home placement leads to a reduction in carer burden; dissimilar findings have been published to date [61]. Contrary to expectations, nursing home placement can substitute existing stressing factors with new ones.

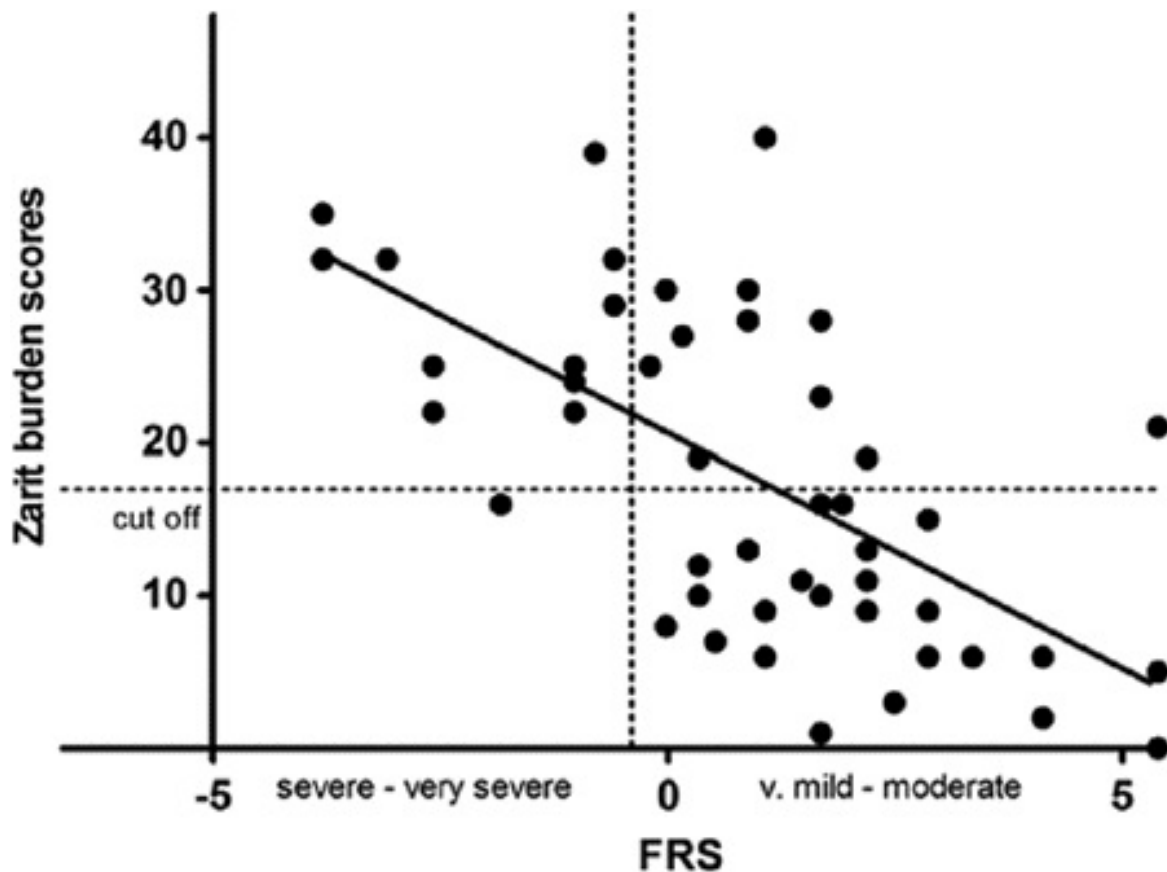


Figure 16.9 FTD carers plotted according to their carer burden scores and patients' dementia severity scores (FRS), demonstrating a significant association between high levels of carer burden and dementia severity. *From:* Mioshi E, Foxe D, Leslie F, *et al.* (2013). The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 27(1), 68–73.

Reproduced with permission from Wolters Kluwer Health.

Differences in reported carer burden can depend on FTD subtype [64], where carers of patients with bvFTD are likely to be more markedly burdened than the carers of aphasic patients (Figure 16.10), who in turn show similar levels of carer burden to those seen in AD carers. In addition, the rate of carer depression tends to be significantly higher amongst bvFTD carers compared with other FTD variants and AD – even though not all carers report depressive symptoms. It is clear that burden is complex and not only dependent on dementia symptoms, or carer-based factors.

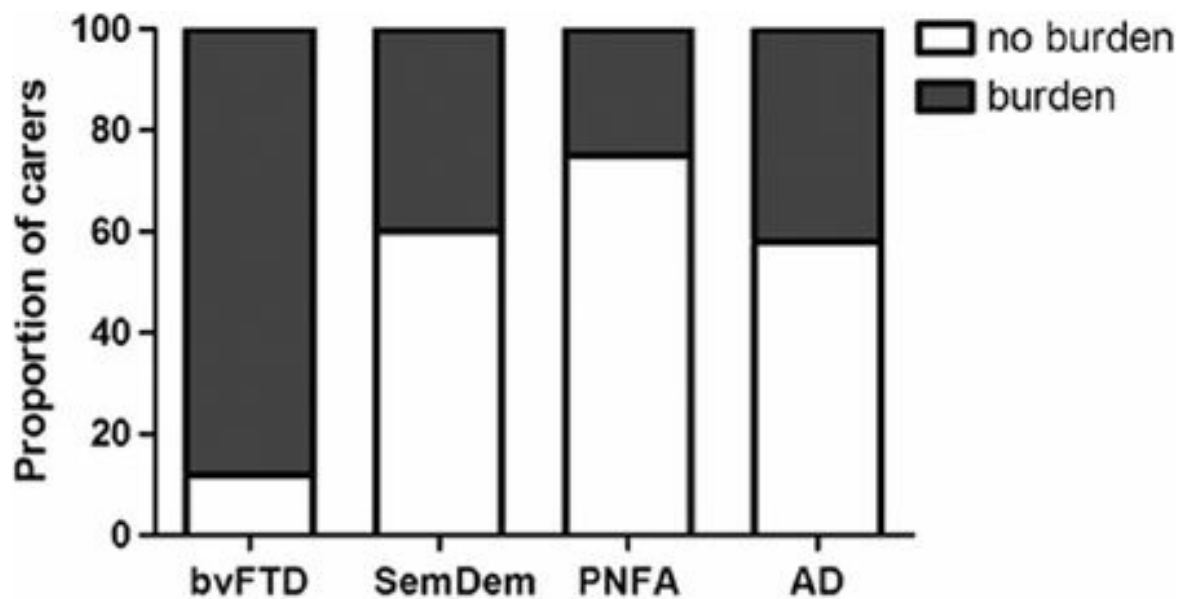


Figure 16.10 Proportion of carers (bvFTD, svPPA [SemDem], nvPPA [PNFA], AD) presenting with burden scores above (high burden) and below cutoffs on the Zarit Burden Interview. *From: Mioshi E, Foxe D, Leslie F, et al. (2013). The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 27(1), 68–73.*

Reproduced with permission from Wolters Kluwer Health.

The similar level of burden reported in nvPPA and AD carers may be due to the similarity of the patients' clinical presentations – rather circumscribed cognitive deficits with little behavioral change, at least for a number of years. It is also possible that the language output difficulties, which are the main impairment in these patients and are also observed in other patient groups, such as post-stroke patients, may be more easily accepted by the carers and those around the patient.

Sadly, the impact of a diagnosis of FTD is not restricted to spousal-carers. Children-carers have also reported marked levels of carer burden, which is indistinguishable from spousal-carers. The main difference seems to lie on the factors driving such burden, which in the children-carers tends to be strongly dependent on their own depressive symptoms [59].

Given the marked levels of carer burden in FTD, it is important that any interventions addressing behavioral management or increasing activity participation be preceded by, or accompanied with, work to increase carers' skills. Our experience has shown that a combined approach that empowers carers' coping skills and targets activity participation of patients will have a more prolonged effect than simply providing strategies to the carers. We have conducted a feasibility study on a structured carer program in FTD, and will pilot a randomized controlled trial in the near future. We expect to find that carers who are equipped with transferrable skills such as problem-solving and thought modification, and seeking support [65] will respond more successfully to any other targeted dementia intervention. It is likely that preparing carers through psychoeducational programs [66] will lead to more efficacious results in other dementia-related interventions such as programs targeting falls' prevention, increased activity participation, and behavioral management, amongst others.

Improving functional abilities in FTD: therapeutic recommendations

Following on from the description and studies of functional disability in FTD, the subsequent obvious question is, *“how do we address these difficulties?”* In this section we will present a summary of current published findings and our own extensive experience in advising on dementia management as well as the feedback from the family carers themselves, compiled over the past 10 years. We will also combine elements of published studies [22, 65–67] examples.

The primary stage of any management plan in FTD should involve education to both formal and family carers about the disease process and

resulting clinical manifestations of symptoms and behaviors [68]. When carers lack clear understanding of the cause of behaviors, frustration, stress, and depression tend to arise. It is very important that carers, especially family carers, understand that the brain changes lead to behavioral changes. More often than not, family carers will attribute some of the patient's difficult behaviors to their own actions, which in turn can lead to an avoidable sense of guilt and distress. Guidance to carers to retain or increase patient activity participation is an iterative process, and has to be preceded by education of the disease symptoms that lead to functional disability. Our extensive clinical experience in running specialist FTD clinics in Cambridge and Sydney has shown that simply providing direct strategies for carers to cope with functional deficits or behavioral symptoms can be short-lived. Instead, we have observed that working in educating the carers on the disease process and symptoms, which lead to behavioral changes and functional deficits, is key to promoting successful skills which will outlast the initial stages post-diagnosis (Figure 16.11). Given the progressive nature of the disease, varying rates of decline between FTD variants, and increased carer burden as the dementia progresses, family carers must be equipped to deal with constant changes and not only with specific advice that may suit one specific situation.

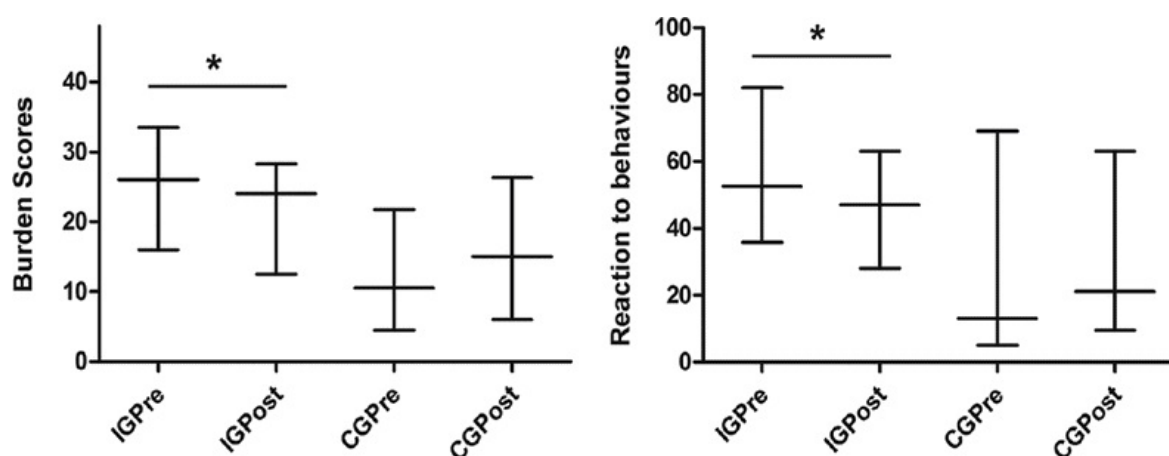


Figure 16.11 Carer burden and carer reaction to patient behavior scores for

the intervention (IG) and control groups (CG), pre- and postintervention or waiting period. *From:* Mioshi E, McKinnon C, Savage S, O'Connor CM, Hodges JR (2013). Improving burden and coping skills in frontotemporal dementia caregivers: a pilot study. *Alzheimer Disease and Associated Disorders*, 27(1), 84–6.

Reproduced with permission from Wolters Kluwer Health.

Crucially, one underlying critical fact that carers need to be educated to understand is not to confront or try to change patients' difficult behaviors, but to learn to accommodate the stereotypical, rigid, or unusual behaviors into their routines to promote patients' participation in activities that are meaningful to them (see Case 1).

Other important strategies to consider in the general management of patients with FTD include environmental modifications and communication strategies. Environmental modification refers to altering aspects of a person's environment for a range of reasons which may include safety (e.g., removing power tools from a shed), behavioral management (e.g., shutting the curtains during school hours to prevent inappropriate interactions with students), or assisting with engagement (e.g., removing any items not relevant to a task to prevent distraction) [69]. Communication strategies involve a range of techniques to assist the person with FTD to understand, and also to assist the person to be understood. Communication strategies may involve changing verbal communication (e.g., providing simple one-step instructions in a clear voice), providing a medium for written communication (e.g., a person with nfvPPA may be mute, but still able to articulate themselves using a tablet computer), using pictures to aid in communication (e.g., using a picture-based recipe to assist a person with svPPA to continue to cook), and using body language (e.g., pointing to objects to aid with an explanation). It is important to note that behaviors

exhibited in FTD are often unchangeable. It is in these situations where carer education focusing on problem-solving strategies, coping strategies, and seeking support are vital (see Case 2).

Each new issue in FTD requiring behavioral management should be considered by taking into account the potential risks involved if the behavior continues, but also how to best utilize the behavior in question to help in keeping the patient engaged in activity participation. As carers become more skilled at assessing each individual situation, their own stress levels may reduce as they are able to recognize when there is a need to change something because of potential hazards, or when it is best to “let it go” and accept the behavior. This approach also has the great benefit of increasing carers’ sense of control of the situation (see Case 3).

Professionals should aim to provide carers with long-lasting abilities to engage patients in activities as the disease progresses, such as proficiency to evaluate situations and activities against patients' current levels of cognitive and behavioral aptitudes. With this in mind, we also recommend some specific strategies that might aid families in understanding the reasoning in adapting tasks or in overcoming situations where the behavior is not preventable. Family carers will have numerous specific questions about everyday issues, and providing them with some direct guidance will increase rapport and trust, as well as help in reducing stress. Most families have been through numerous professionals to obtain a definitive FTD diagnosis, and realizing that the professional really understands FTD can have a reassuring effect that should not be underestimated.

Management strategies based on specific instrumental ADLs are presented in [Tables 16.1](#) and [16.3](#), and basic ADLs are presented in [Tables 16.2](#) and [16.4](#).

Conclusions/summary

We are clearly better equipped to address everyday issues raised by FTD families than 10 years ago. We also now have moved from a limited range of ADL scales (developed in the context of physical disability settings) used in research and clinical settings, to dementia-specific ADL assessments. These efforts have culminated in standardized and valid methods to determine dementia severity in FTD that can aid in prognosis; these novel measures also allow us to monitor pharmacologic and non-pharmacologic studies more confidently.

It is indeed exciting to observe that dementia management has become an area of increased interest in FTD, with new studies emerging at a stimulating pace. This will hopefully lead to a broader, yet scientifically based, understanding of the impact of FTD in patients and families. These orchestrated efforts in turn will produce evidence-based guidelines for the management of dementia in FTD, which have the potential to make a real impact on those affected by FTD beyond a diagnosis and specialist settings.

We still have a long path ahead before tailored treatments for each stage of the disease, FTD subtype, and non-pharmacologic therapies are developed, trialed, and translated into the health services. Yet, the road ahead for dementia management in FTD seems less dark than a few years ago.

Cases

Case 1 Andrew has svPPA. He has a rigid breakfast preparation routine where he cuts up fruit for himself and his wife (in meticulous cubes), followed by a thorough kitchen tidy-up. One morning they

have a doctor's appointment to attend and Jane, Andrew's wife, wants him to skip the fruit routine as she is worried about being late for the appointment. Andrew cannot understand why his wife is trying to stop him from conducting his routine, and is becoming agitated. Andrew's wife is becoming more stressed about missing the appointment and raises her voice. Although Andrew is having difficulty understanding why, he hears her raised voice and sees she is trying to stop his routine. This in turn leads to increased agitation, and he reacts by shouting angrily at his wife. They end up missing the appointment and Andrew manages to get on with his routine.

What could be done in this scenario: Jane could wake Andrew up earlier that morning to allow time for him to conduct his routine as usual, leaving them time to attend the appointment afterwards. Accommodating for Andrew's behavior in this situation, instead of trying to stop it, would help reduce the carer's concern about missing the appointment, and also prevent Andrew's agitation from a change in his fixed routine. This would also have avoided the escalation to a verbally aggressive outburst from Andrew in reaction to his wife's stress-filled communication. Importantly, this strategy promotes Andrew's ability to participate in daily activities.

Case 2 Trevor is 64 years old and has svPPA (semantic dementia). He enjoys talking with strangers, demonstrating to people his lunge-walking abilities, and has developed an innocent but persistent fascination with children. When Trevor and his wife Sally are out in public, Trevor may exhibit any of these behaviors, including approaching children they do not know to talk to them or watch them play. Sally has come to dread leaving the house with Trevor, and has

been restricting their participation in previously enjoyed leisure activities such as going out to dinner or taking the grandchildren to the park.

What could be done in this scenario: Sally has a number of options to try out in this situation, as seen in [Table 16.3](#). She could try to avoid peak times at the supermarket (where they usually go together), and other public spaces, as Trevor tends to demonstrate his lunge-walks when surrounded by people. Sally could also carry cards explaining Trevor's behavior (some dementia associations distribute these freely, or she could have them printed at home/friends'), which she can hand to the parents as Trevor interacts and chats away to their children. Finally, Sally could also try to engage family, friends, or services to be with Trevor while she goes out to the playground with the grandchildren, for instance. It is important to work with Sally on the need to create spaces in her week just for herself, when she can go to places alone, or with others, but without Trevor.

Case 3 Peter is 58 years old and has bvFTD. Over the past year Peter has developed an obsession with collecting the seeds from any fruit he eats and hiding them in his pockets or in selected places around the house. When this behavior began, Peter's wife Sandra found this very frustrating and annoying, spending time berating Peter in the hope he would change his behavior. Over time, however, Sandra has learnt to accept this behavior as it engages Peter, and does not pose any risk to him or family members. Occasionally, when Peter is sleeping or in another room, Sandra will quietly remove some of the seeds from around the house. Peter

never notices when seeds have been removed, so does not react in a negative manner. Sandra has learned that there is no need to change this type of behavior (it is safe); it is less distressing for them both to let it happen (there is no confrontation) and the best way to keep it under control is to monitor the outcomes without his knowledge (being in control by removing some of the seeds when he is not around).

References

1. James AB. Activities of daily living and instrumental activities of daily living. In: Crepeau EB, Cohn ES, Schell BAB, editors. *Willard Spackman's Occupational Therapy*, 11th edn. Baltimore: Lippincott Williams & Wilkins; 2009. p. 538–40.
2. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;**9**(3):179–86.
3. Sonn U. Longitudinal studies of dependence in daily life activities among elderly persons. *Scand J Rehabil Med* 1996;**34**:1–35.
4. Mesulam MM, Wieneke C, Thompson C, Rogalski E, Weintraub S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain* 2012;**135**:1537–53.
5. Blair M, Marczyński CA, Davis-Faroque N, Kertesz A. A longitudinal study of language decline in Alzheimer's disease and frontotemporal dementia. *J Int Neuropsychol Soc* 2007;**13**:237–45.
6. Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and disease progression in frontotemporal dementia. *Neurology* 2010;**74**:1591–7.

-
7. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;**43**:2412–4.
-
8. Lima-Silva TB, Bahia VS, Carvalho VA, Guimaraes HC, Caramelli P, Balthazar M, *et al.* Translation, applicability and cross-cultural adaptation of the Brazilian version of the Frontotemporal Dementia Rating Scale (FTDFRS). *Dement Neuropsychol* 2013;**7**:387–96.
-
9. Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, *et al.* Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* 2008;**131**:2957–68.
-
10. Hornberger M, Piguet O, Kipps C, Hodges JR. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology* 2008;**71**(19):1481–8.
-
11. Mioshi E, Kipps CM, Dawson K, Mitchell J, Graham A, Hodges JR. Activities of daily living in frontotemporal dementia and Alzheimer disease. *Neurology* 2007;**68**:2077–84.
-
12. Mioshi E, Hodges JR. Rate of change of functional abilities in frontotemporal dementia. *Dement Geriatr Cogn Disord* 2009;**28**:419–26.
-
13. Wicklund AH, Johnson N, Rademaker A, Weitner BB, Weintraub S. Profiles of decline in activities of daily living in non-Alzheimer dementia. *Alzheimer Dis Assoc Disord* 2007;**21**(1):8–13.
-
14. Raskovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;**134**:2456–77.
-
15. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;**51**:1546–54.
-

16. Lima-Silva TB, Bahia VS, Nitrini R, Yassuda MS. Functional status in behavioral variant frontotemporal dementia: a systematic review. *Biomed Res Int* 2013;**2013**:1–7.

17. Garcin B, Lillo P, Hornberger M, Piguet O, Dawson K, Nestor PJ, *et al.* Determinants of survival in behavioral variant frontotemporal dementia. *Neurology* 2009;**73**(20):1656–61.

18. Rascovsky K, Salmon DP, Lipton AM, Leverenz JB, Decarli C. Rate of progression differs in frontotemporal dementia and Alzheimer disease. *Neurology* 2005;**65**:397–403.

19. Kipps CM, Nestor PJ, Dawson CE, Mitchell J, Hodges JR. Measuring progression in frontotemporal dementia: implications for therapeutic interventions. *Neurology* 2008;**70**(22):2046–52.

20. De Simone V, Kaplan L, Patronas N, Wassermann EM, Grafman J. Driving abilities in frontotemporal dementia patients. *Dement Geriatr Cogn Disord* 2007;**23**(1):1–7.

21. Jonah BA, Thiessen R, Au-Yeung E. Sensation seeking, risky driving and behavioral adaptation. *Accid Anal Prev* 2001;**33**(5):679–84.

22. Merrilees J, Ketelle R. Advanced practice nursing: meeting the caregiving challenges for families of persons with frontotemporal dementia. *Clin Nurse Spec* 2010;**24**(5):245–51.

23. Ghosh A, Dutt A. Utilisation behaviour in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2010;**81**(2):154–6.

24. Mioshi E, Kipps CM, Hodges JR. Activities of daily living in behavioural variant frontotemporal dementia. *Alzheimer Dis Assoc Disord* 2009;**23**(1):70–6.

25. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant

frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol* 2011;**10**:162–72.

26. Merrilees J, Dowling GA, Hubbard E, Mastick J, Ketelle R, Miller BL. Characterization of apathy in persons with frontotemporal dementia and the impact on family caregivers. *Alzheimer Dis Assoc Disord* 2013;**27**(1):62–7.

27. Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. *CNS Drugs* 2010;**24**(5):375–98.

28. Litvan I. Therapy and management of frontal lobe dementia patients. *Neurology* 2001;**56**(Suppl 4):S41–5.

29. Piguet O. Eating disturbance in behavioural-variant frontotemporal dementia. *J Mol Neurosci* 2011;**45**(3):589–93.

30. Farmer J, Grossman M. Frontotemporal dementia: an overview. *Alzheimers Care Q* 2005;**6**(3):225–32.

31. Le Rhun E, Richard F, Pasquier F. Natural history of primary progressive aphasia. *Neurology* 2005;**65**(6):887–91.

32. Bier N, Macoir J, Joubert S, Bottari C, Chayer C, Pigot H, *et al.* Cooking “Shrimp a la Creole”: a pilot study of an ecological rehabilitation in semantic dementia. *Neuropsychol Rehabil* 2011;**21**(4):455–83.

33. Miller BL, Darby AL, Swartz JR, Yener GG, Mena I. Dietary changes, compulsions and sexual behavior in frontotemporal dementia. *Dementia* 1995;**6**:195–9.

34. Kashibayashi T, Ikeda M, Komori K, Shinagawa S, Shimizu H, Toyota Y, *et al.* Transition of distinctive symptoms of semantic dementia during longitudinal clinical observation. *Dement Geriatr Cogn Disord* 2010;**29**(3):224–32.

-
- 35.** Mesulam MM. Primary progressive aphasia: a language-based dementia. *N Engl J Med* 2003;**349**(16):1535–42.
-
- 36.** Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* 2001;**70**:323–32.
-
- 37.** Green HAC, Patterson K. Jigsaws-a preserved ability in semantic dementia. *Neuropsychologia* 2009;**47**(2):569–76.
-
- 38.** Seeley WW, Bauer AM, Miller BL, Gorno-Tempini ML, Kramer JH, Weiner M, *et al.* The natural history of temporal variant frontotemporal dementia. *Neurology* 2005;**64**(8):1384–90.
-
- 39.** Jang J, Cushing N, Clemson L, Hodges JR, Mioshi E. Activities of daily living in progressive non-fluent aphasia, logopenic progressive aphasia and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012;**33**:354–60.
-
- 40.** Cushing N, Jang J, O'Connor CM, Burrell JR, Clemson L, Hodges JR, *et al.* Disability in atypical parkinsonian syndromes is more dependent on memory dysfunction than motor symptoms. *Parkinsonism Relat Disord* 2013;**19**(4):436–40.
-
- 41.** Gorno-Tempini ML, Hillis A., Weintraub S, Kertesz A, Mendez M, Cappa SF, *et al.* Classification of primary progressive aphasia and its variants. *Neurology* 2011;**76**(11):1006–14.
-
- 42.** Kertesz A, Martinez-Lage P, Davidson W, Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. *Neurology* 2000;**55**(9):1368–75.
-
- 43.** Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, *et al.* Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol* 2004;**55**(3):335–46.
-

-
- 44.** Leyton CE, Villemagne VL, Savage S, Pike KE, Ballard KJ, Piguet O, *et al.* Subtypes of progressive aphasia: application of the international consensus criteria and validation using B-amyloid imaging. *Brain* 2011;**134**(10):3030–43.
-
- 45.** Mesulam M, Wicklund A, Johnson N, Rogalski E, Leger GC, Rademaker A, *et al.* Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Ann Neurol* 2008;**63**(6):709–19.
-
- 46.** Rabinovici GD, Jagust WJ, Furst AJ, Ogar JM, Racine CA, Mormino EC, *et al.* Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Ann Neurol* 2008;**64**(4):388–401.
-
- 47.** Rohrer JD, Ridgway GR, Crutch SJ, Hailstone J, Goll JC, Clarkson MJ, *et al.* Progressive logopenic/phonological aphasia: erosion of the language network. *Neuroimage* 2010;**49**(1):984–93.
-
- 48.** Leyton CE, Hsieh S, Mioshi E, Hodges JR. Cognitive decline in logopenic aphasia: more than losing words. *Neurology* 2013;**80**(10):897–903.
-
- 49.** Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain* 2005;**128**(9):1996–2005.
-
- 50.** Mathuranath P, Xuereb J, Bak T, Hodges J. Corticobasal ganglionic degeneration and/or frontotemporal dementia? A report of two overlap cases and review of literature. *J Neurol Neurosurg Psychiatry* 2000;**68**(3):304–12.
-
- 51.** Mimura M, White RF, Albert ML. Corticobasal degeneration: neuropsychological and clinical correlates. *J Neuropsychiatry Clin Neurosci* 1997;**9**(1):94–8.
-
- 52.** Murray R, Neumann M, Forman MS, Farmer J, Massimo L, Rice A, *et al.* Cognitive and motor assessment in autopsy-proven corticobasal degeneration. *Neurology* 2007;**68**(16):1274–83.
-
- 53.** Mochizuki A, Ueda Y, Komatsuzaki K, Tsuchiya K, Arai T, Shoji S.

Progressive supranuclear palsy presenting with primary progressive aphasia – clinicopathological report of an autopsy case. *Acta Neuropathol* 2003;**105**(6):610–14.

54. Diehl-Schmid J, Bornschein S, Pohl C, Forstl H, Kurz A, Jahn T. Cognitive decline in the behavioural variant of frontotemporal dementia. *Int Psychogeriatr* 2011;**23**(2):230–7.

55. Josephs KA, Whitwell JL, Weigand SD, Senjem ML, Boeve BF, Knopman DS, *et al.* Predicting functional decline in behavioural variant frontotemporal dementia. *Brain* 2011;**134**(Pt 2):432–48.

56. Bouwens SFM, van Heugten CM, Verhey FRJ. Association between cognition and daily life functioning in dementia subtypes. *Int J Geriatr Psychiatry* 2009;**24**:764–9.

57. Osher JE, Wicklund AH, Rademaker A, Johnson N, Weintraub S. The minimal state examination in behavioral variant frontotemporal dementia and primary progressive aphasia. *Am J Alzheimers Dis Other Dement* 2008;**22**(6):468–73.

58. Mioshi E, Hodges JR, Hornberger M. Neural correlates of activities of daily living in frontotemporal dementia. *J Geriatr Psychiatry Neurol* 2013 Mar;**26**(1):51–7.

59. Kaizik C, O'Connor C, McKinnon C, Oyeboode J, Piguet P, Hodges J, Mioshi E. The burden of care in FTD: the under-reported impact on child-carers. *Am J Neurodegener Dis* 2014;**3**(Suppl 1):361.

60. Riedijk SR, De Vugt ME, Duivenvoorden HJ, Niermeijer MF, van Swieten JC, Verhey FRJ, *et al.* Caregiver burden, health-related quality of life and coping in dementia caregivers: a comparison of frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2006;**22**:405–12.

61. Mioshi E, Bristow M, Cook R, Hodges JR. Factors underlying caregiver

stress in frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2009;**27**:76–81.

62. Bristow M, Cook R, Erzinclioglu S, Hodges J. Stress, distress and mucosal immunity in carers of a partner with fronto-temporal dementia. *Aging Ment Health* 2008;**12**(5):595–604.

63. Boutoleau-Bretonniere C, Vercelletto M, Volteau C, Renou P, Lamy E. Zarit burden inventory and activities of daily living in the behavioral variant of frontotemporal dementia. *Dement Geriatr Cogn Disord* 2008;**25**:272–7.

64. Mioshi E, Foxe D, Leslie F, Savage S, Hsieh S, Miller L, *et al.* The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2013;**27**(1):68–73.

65. Mioshi E, McKinnon C, Savage S, O'Connor CM, Hodges JR. Improving burden and coping skills in frontotemporal dementia caregivers: a pilot study. *Alzheimer Dis Assoc Disord* 2013;**27**(1):84–6.

66. Diehl J, Mayer T, Forstl H, Kurz A. A support group for caregivers of patients with frontotemporal dementia. *Dementia* 2003;**2**(2):151–61.

67. Gitlin LN, Winter L, Burke J, Chernett N, Dennis MP, Huack WW. Tailored activities to manage neuropsychiatric behaviors in persons with dementia and reduce caregiver burden: a randomized pilot study. *Am J Geriatr Psychiatry* 2008;**16**(3):229–39.

68. Hall GR, Shapira J, Gallagher M, Denny SS. Managing differences: care of the person with frontotemporal dementia. *J Gerontol Nurs* 2013;**39**(3):10–14.

69. Yokota O, Fujisawa Y, Takahashi J, Terada S, Ishihara T, Nakashima H, *et al.* Effects of group-home care on behavioral symptoms, quality of life, and psychotropic drug use in patients with frontotemporal dementia. *J Am Med Dir Assoc* 2006;**7**(5):335–7.

70. Massimo L, Grossman M. Patient care and management of frontotemporal lobar degeneration. *Am J Alzheimers Dis Other Demen* 2008;**23**(2):125–31.

71. Bozeat S, Lambon Ralph MA, Patterson K, Hodges JR. The influence of personal familiarity and context on object use in semantic dementia. *Neurocase [Internet]* 2002;**8**(1–2):127–34. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11997491>.

Chapter 17

Practical management of frontotemporal dementia



Edward D. Huey and Masood Manoochehri

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

The frontotemporal dementias (FTD) typically present as a specific clinical syndrome, but as these diseases progress, patients usually develop a wider set of cognitive, behavioral, language, and motor symptoms that affect their daily living. Clinicians can face a changing cluster of symptoms whose management is often best served by a multidisciplinary approach. As there are no disease-modifying medications to stop the progression of FTD, the clinician's familiarity with an array of pharmacologic and non-pharmacologic tools can guide the practical management of the diverse symptoms that will likely be encountered throughout the disease course.

Initial clinic contact and early-stage management

An early and accurate diagnosis is an important starting point for the practical management of FTD. For many reasons, including symptom overlap with psychiatric disorders and a lack of familiarity with FTD in mental health settings, this issue continues to plague the field, with mood disorders and Alzheimer's disease (AD) being common misdiagnoses of FTD [1]. Frustration with the process of diagnosis is reported as a major complaint and source of stress for FTD caregivers [2]. More detailed and sensitive criteria have recently been proposed for diagnosing behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA) [3, 4]. The familiarity of clinicians with the salient features of the diseases as outlined in these criteria should help detect FTD at an earlier stage.

Early symptoms of bvFTD commonly include apathy, socially inappropriate behavior, loss of empathy, perseverative speech or behaviors, dietary changes, and executive function deficits with relatively preserved memory and visuospatial function [3]. Functionally, difficulty with complex tasks such as managing correspondences and planning finances characterize mild stages of bvFTD [5].

Patients with bvFTD are at particular risk for being misdiagnosed with a psychiatric disorder [6]. Clinicians should be aware of “red flags” that can help with an accurate diagnosis. For example, patients often exhibit the apathy and decreased energy seen in major depressive disorder, but rarely show emotional distress or depressed mood. Patients with repetitive and stereotyped behaviors usually do not experience the anxiety and obsessions that are characteristic of obsessive–compulsive disorder. Other indications of neurodegenerative disease may include the presence of cognitive dysfunction, the absence of previous psychiatric history, and an unusual psychiatric presentation [7].

In the earliest phases of PPA, patients may describe increasingly effortful speech and word-finding difficulty. General cognitive and

functional abilities can be largely spared, with preserved performance on formal tests outside of language function [8]. Clinicians sometimes attribute speech deficits to emotional distress or dysfunctional vocal cords. New criteria developed for diagnosing PPA have been shown to be sensitive to early detection of characteristic cortical atrophy patterns [8].

An early diagnosis of FTD is important for several reasons. First, it allows the patient to seek resources that may help manage symptoms. Second, accurate diagnosis provides a framework for families to understand the often dramatic changes in personality and behavior that occur to their loved ones. Understanding behavioral symptoms as a by-product of neurodegenerative disease, and not deliberate intention, is usually helpful for families. FTD caregivers identify thorough explanation of the diagnosis and support by a knowledgeable physician as important interventions [9]. Finally, future disease-modifying treatments will most likely be effective early in the disease process. Delays in diagnosis will prevent patients from their best chance at benefit.

At this stage, clinicians should also be prepared to discuss disease course with the patient and caregiver. Given the heterogeneity in clinical presentation and pathology, it has been difficult to establish a single model of disease progression in FTD. Progressive neurodegeneration leads to greater behavioral and cognitive deficits in both bvFTD and PPA, and often to motor deficits as well. These symptoms reduce the capacity of patients to live independently, making them dependent on the caregiver. Ultimately, the accumulation of cognitive and neurologic deficits leads to reduced lifespan.

The time course for these changes is variable. Estimates of survival have been reported to be from 3 to 14 years after diagnosis [10]. There is no evidence that disease severity at diagnosis, age of onset, or demographic characteristics affect survival in FTD. However, patients presenting with motor neuron disease (MND) symptoms, genetic mutations, and co-

occurring behavioral and language symptoms decline more rapidly [11, 12]. Greater cognitive abilities and language fluency at diagnosis correlate with slower progression in PPA [13]. New biomarkers may soon also be able to help clinicians with prognosis [14]. Communicating the progressive nature of FTD allows for patients and families to mentally and emotionally prepare for further cognitive and functional declines. Families may also opt to begin handling legal and financial issues while the patient has intact cognitive abilities. At this stage, clinicians can also discuss the possibility of genetic testing and brain autopsy, and the implications that these may have for the family.

The clinician–caregiver relationship is an essential part of managing FTD. Patients often exhibit lack of insight into the nature of their behavioral and cognitive deficits [15]. Speech deficits in PPA can also present a barrier to communication with the physician. Caregivers therefore are usually the best source of information about behavioral and cognitive changes. Clinicians should seek to establish supportive relationships with caregivers at the outset in order to facilitate the management of symptoms. This includes introducing educational and supportive local resources. Referrals to a genetic counselor should be made if genetic testing is under consideration. Referral to nationwide organizations, such as the Association for Frontotemporal Degeneration (AFTD) in the USA, are helpful [16]. Clinicians can also suggest that caregivers maintain a symptom diary. This can be a useful tool to track the evolution of and triggers for symptoms, especially behavioral symptoms, as the disease progresses, and to see the effects of therapeutic interventions as they are introduced [17].

Management at middle stages

The middle stages of FTD are generally characterized by a widening circle of behavioral symptoms, increasing cognitive dysfunction, and greater decline in functional abilities. The FTLD–Clinical Dementia Rating and Frontotemporal Dementia Rating Scales are tools that can help clinicians track disease severity and symptoms [5, 18]. Neuropsychological testing can help clinicians track the rate of cognitive decline.

Patients with PPA generally experience broader language impairments and a deteriorated ability to communicate. Instruments such as the Progressive Aphasia Severity Scale (PASS) can help clinicians track impairment in language domains and functional communication [19]. Patients with non-fluent variant PPA (nfvPPA) will generally have involvement of other areas of cognition besides language, especially executive dysfunction. Patients with semantic variant PPA (svPPA), associated with anterior temporal impairment, will usually present with a behavioral syndrome in addition to their semantic deficits. The degree to which this is due to involvement of frontal structures involved in behavioral regulation, the role of the anterior temporal lobes in behavior, and the effects of semantic loss on behavior is not currently known [20]. Although functional abilities inevitably decline, there is some evidence that PPA patients are able to maintain relative independence in living for longer than patients with bvFTD [5].

Caregivers usually experience increasing burden and strain as the disease progresses. As the patient loses functional abilities, caregivers must take on tasks such as refilling prescriptions, scheduling and taking patients to appointments, and handling correspondence [21]. In patients with behavioral symptoms, the caregiver may need to eliminate hazards in the home or provide close supervision of the patient during meals as patients can put excessive and even dangerous amounts of food in their mouths. Communication may become very limited, either due to language symptoms

or as a symptom of apathy. Home health aides can provide some practical help in managing the patient's symptoms, giving caregivers much-needed respite.

Continuity of care is an important part of managing FTD. Patients often show fluctuation in behavioral symptoms, with new ones developing over time and others worsening. Frequent clinical visits can help to manage these evolving symptoms on a timely basis. Even if no medicines are prescribed or altered, a visit in which problematic behaviors and non-pharmacologic strategies are discussed can be very valuable for the patient and caregiver. A collaborative relationship with the patient's primary care provider should also be maintained between visits. Keeping an accurate log of symptoms can help clinicians differentiate disease fluctuations from possible side effects of medications or other causes.

Pharmacologic management

Given the diversity of symptoms and pathologic heterogeneity of FTD, it is perhaps not surprising that pharmacologic treatment of the symptoms of FTD needs to be tailored to the patient. Cognitive and language impairments and certain behavioral symptoms in FTD are generally not amenable to pharmacologic treatment. The behavioral symptoms that are not usually improved with medication treatment include reduced empathy, deficits in social cognition, and apathy. Important goals of pharmacotherapy in FTD include educating the family as to what symptoms the clinician is targeting with medication treatment, that medications can ameliorate, but generally not remove, behavioral symptoms, and the creative integration of pharmacologic and non-pharmacologic treatments (see [Table 17.1](#)). For example, medications can be used to attempt to reduce compulsive pacing

and wandering, but measures should also be undertaken to prevent elopement or minimize its consequences, e.g., locked doors and identification bracelets.

Table 17.1 Symptomatic treatments for FTD spectrum disorders

Domain	Symptom	Pharmacologic tx	Non-pharmacologic tx
Language symptoms	Expressive aphasia	None	Speech therapy; caregiver education; compensatory tools such as scripts and augmentative and alternative communication devices (AACs)
	Naming and comprehension deficits	None	Speech therapy; caregiver education on communication methods
Behavioral and neuropsychiatric symptoms	Apathy and inertia	None	Caregiver education and support; supervision and direction
	Agitation, aggression, and impulsive behaviors	Antidepressants, atypical antipsychotics	Caregiver education; monitoring and removal of environmental

			triggers, caregiver oversight of physical and social environment
	Lack of empathy and sympathy	None	Caregiver education; caregiver support groups
	Perseverative and ritualistic behaviors	Antidepressants	Caregiver oversight; toleration of behavior; distraction
	Compulsive eating and dietary abnormalities	Antidepressants	Caregiver oversight of diet; environmental and physical modifications; consultation with dietician
Cognitive symptoms	Executive dysfunction	Evaluation for medications that could impair cognition	Consultation with cognitive rehabilitation therapist; compensatory tools
Motor symptoms	Falls	Evaluation for medications that could contribute to parkinsonism, orthostasis, or balance impairment	Environmental modifications; physical therapy; consultation with occupational therapist; walkers and/or wheelchairs
	Dystonia	Botulinum toxin	Splinting; physical

	injections	therapy
Parkinsonism	Carbidopa/levodopa trial (in part, for diagnostic purposes)	Caregiver support

Antidepressants can reduce some behavioral symptoms, particularly disinhibition, compulsive behaviors, and hyperorality. Although there have been few double-blind, placebo-controlled studies, case series and open label studies have tested the effects of selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram) and trazodone [22]. FTD demonstrates significant serotonergic deficits in imaging and autopsy studies [23]. Despite the lack of large-scale systematic clinical trials, there is some evidence for their symptomatic efficacy [24]. FTD patients are generally physically younger and healthier than other dementia patients and can usually tolerate doses similar to those used for psychiatric indications. Potential side effects include nausea, headache, and sexual symptoms, but usually these medications are well tolerated in FTD, and some adverse effects, e.g., decreased appetite or libido, may even be beneficial. Antidepressant use has been associated with an increased rate of falls in elderly patients and patients with Parkinson's disease [25]. While it has not been directly assessed, this finding suggests that antidepressants should be used cautiously with disorders such as progressive supranuclear palsy (PSP) for which falls are a prominent symptom. The choice of a particular antidepressant is often informed by the receptor profile and medication interactions of the medication. Sertraline (Zoloft) and citalopram (Celexa) are SSRIs with minimal effect on other receptors and cytochrome P450 enzymes. Although recent evidence showing

QT prolongation with citalopram use, especially at higher doses, has limited its use.

Atypical antipsychotics can be prescribed to treat disinhibition and agitation. There have been few formal studies of these medications as symptomatic treatments in FTD. However, this class of medications has historically been used to treat psychosis and agitation in patients with dementia from AD [26]. Quetiapine (Seroquel) is often a first-line agent because of its relatively low D2 receptor occupancy, given the increased risk of extrapyramidal symptoms (EPS) in FTD. Its use, however, is associated with significant sedation and should be used cautiously in patients with orthostatic hypotension owing to its anti-histaminic, -adrenergic, and -muscarinic actions, and clinicians should be familiar with prescribing the other agents in this class of medications. The therapeutic and adverse effects of this class of medications can generally be predicted by their profile of receptor blockade. Typical antipsychotic medications are generally not used because of their increased risk of EPS. Olanzapine (Zyprexa) is rarely used in FTD because it is often associated with an increase in appetite, due to its blockade of H1 and 5-HT_{2C} and 3 receptors. Clozapine (Clozaril) has minimal D2 occupancy, but has many potential adverse effects, including agranulocytosis, requiring blood draws and limiting its use. Risperidone (Risperdal) has a relatively higher D2 occupancy, and thus higher incidence of EPS than most of the other atypical antipsychotics, but it appears to reduce agitation with less sedation than quetiapine and can be useful in patients who do not tolerate quetiapine because of excessive sedation. Clinicians should prescribe these medications with caution, as their use in elderly dementia patients has been linked to a 1.5- to 1.7-fold increased risk of mortality and a black box warning from the US Food and Drug Administration (FDA) [27]. The cause of this increased mortality is incompletely understood, but is linked to an

increased risk of cerebrovascular events. Evidence indicates that patients with AD do not tolerate the high doses of antipsychotic medication that are used to treat schizophrenia. Furthermore, beyond a certain dose, e.g., the equivalent of approximately 2 mg of risperidone, there is a minimal increase in efficacy in treating agitation and psychosis in AD [26]. However, it is unclear how this literature translates to FTD, in which the patients are generally younger and healthier than AD patients. There is little evidence on length of treatment for both antidepressants and antipsychotic medications. In general, patients should be evaluated for continued need for medications for behavioral symptoms, especially for antipsychotic medications given their increased mortality. Some experts have argued that a discontinuation trial of antipsychotic medication should be considered for patients whose neuropsychiatric symptoms have been in remission for three to six months [27]. However, emerging evidence has shown in patients with AD that agitation appears to be a symptom that often does not spontaneously remit and discontinuation of antipsychotic medications results in a recurrence of symptoms [28].

Acetylcholinesterase inhibitors (AChEIs) are prescribed for up to 40% of FTD patients [29]. These medications are used in AD, in which the cholinergic system is disrupted. In FTD, the relatively intact cholinergic system presents a poor target for these medications. Clinical studies do not support their use as effective symptomatic treatments for FTD, and one study has documented worsening behavioral symptoms [22]. These considerations have prompted recommendations to avoid treating FTD with AChEIs [30]. Prescribing these medications may be warranted in cases of diagnostic uncertainty with AD or logopenic variant PPA, which usually exhibits AD pathology.

Memantine is a non-competitive *N*-methyl *D*-aspartate (NMDA) antagonist approved for use in AD. It is prescribed for 10–15% of FTD

patients [29]. Initial positive case reports with bvFTD patients spurred hope for the use of memantine in FTD. Since then, however, several placebo-controlled studies have shown no therapeutic effects of memantine on cognition or behavior [31, 32], with one study showing adverse effects on cognition [31].

A complete review of the pharmacologic treatment of the motor syndromes associated with FTD is beyond the scope of this review and readers are directed to other sources [33, 34]. However, a few themes emerge in relation to the interaction of motor and non-motor symptoms of these disorders. Patients with FTD-ALS (amyotrophic lateral sclerosis) should be evaluated for possible riluzole (Rilutek) treatment. While cognitive impairment is not necessarily a contraindication for riluzole treatment, clinicians need to consider issues such as medication compliance and effects of cognitive impairment on quality of life in the decision. Pseudobulbar affect can be a prominent symptom in MND and can complicate the diagnostic evaluation of patients with FTD-ALS. If problematic to patients, this symptom can be treated with serotonergic antidepressants or dextromethorphan/quinidine (Nuedexta). Most patients with PSP and corticobasal degeneration (CBD) will not have a significant or sustained response to levodopa treatment [35], but most experts recommend a trial of levodopa treatment, in part for diagnostic purposes [35].

Other pharmacologic treatments for FTD are under investigation. Lithium, most commonly used to treat bipolar disorder, inhibits tau hyperphosphorylation [36]. However, it was not tolerated at doses used to treat bipolar disorder in a trial for PSP [37]. There is theoretical evidence to suggest that dopaminergic augmentation may represent a future symptomatic treatment for FTD. FTD patients exhibit low levels of cerebrospinal fluid dopamine metabolites and reduced dopamine

transporters in the caudate [23]. Executive function deficits in attention-deficit hyperactivity disorder are effectively treated with dopamine augmentation. One study has shown a reduction in risk-taking behavior following treatment with methylphenidate, a stimulant that enhances synaptic dopamine [22]. A medication that increases prefrontal dopamine levels, tolcapone, is currently under investigation as a symptomatic treatment for FTD [38]. Molecular mediators of social cognition may offer another approach in treating FTD. Administration of oxytocin, a neuropeptide implicated in human bonding and trust, leads to increased empathy and cooperative behavior in normal adults [39]. An initial test of oxytocin as a possible therapeutic agent for bvFTD yielded promising results. Small improvements were seen across a wide set of behavioral symptoms [40], leading to a dosing study to test the safety and tolerability of intranasal oxytocin [41].

Non-pharmacologic interventions

While particular behavioral symptoms may improve with pharmacologic treatment, managing FTD relies in large part on a diversity of non-pharmacologic interventions (see also [Chapter 16](#)). Environmental modifications, compensatory tools, rehabilitation therapies, and behavioral interventions can all play a role in helping to facilitate life functioning for the patient and family. As in the introduction of medications, the particular interventions to be utilized will depend on the specific symptoms and types of impairments of the individual patient.

Cognitive impairments

Early cognitive impairment in FTD is usually secondary to deficits in executive function [3]. The term “executive function” encompasses more complex cognitive abilities including reasoning, abstraction, and mental flexibility. Deficits in these abilities frequently cause difficulty for patients with mentally demanding jobs that involve planning and problem-solving, eventually causing them to take on less demanding positions at work or into early retirement. At home, these deficits can manifest in difficulty with tasks such as managing finances, preparing complex meals, and planning trips.

To compensate for some of these functional impairments, families may need to adjust roles. The primary responsibility for long-term legal, financial, and healthcare decisions often shifts to the caregiver. Caregiver supervision may be needed to help ensure the safe completion of more complex activities of daily living. A symptom of FTD is behavioral rigidity and difficulty learning new behaviors or altering behaviors based on feedback. Patients’ families should be educated to lower their expectations about how much behavioral change they can expect from reasoned debate with FTD patients, even when the patient states that he or she understands and will alter their behavior.

Cognitive rehabilitation professionals also have expertise that may help ease the effects of cognitive impairment in FTD. The progressive nature of FTD precludes adopting the approaches often used with stroke and traumatic brain injury patients. Remediation of skills and a return to normal, independent functioning is not a viable goal. However, patients can benefit from being introduced to compensatory techniques that can help maintain life functioning for the patient and the family. Daily planning tools can help organize the steps needed to complete particular job-related tasks. Checklists and home assessments may be effective in helping to avoid hazardous outcomes at home or at work. Routines that take advantage of the relative preservation of memory seen in FTD may also be suggested. A

thorough assessment of the particular deficits and life activities of the patient can lead cognitive rehabilitation professionals to suggest specific compensatory remedies.

Cognitive impairments can present a particular hazard in patients with FTD-ALS. Because of their impaired judgment and attention, these patients are particularly at risk for reduced compliance with feeding tube procedures, non-invasive ventilation, and occupational and physical therapy [42]. Physical safety can be compromised if they are unable to understand how to prevent and cope with falls or choking episodes. Patients may not be able to use assistive technology such as computer interfaces that require learning and training. As deteriorating cognitive function can compromise the ability to make the various healthcare decisions that are required in ALS, families should discuss plans for future action as early as possible in the disease course.

Communication impairments

Communication impairments in FTD are of two types. In bvFTD, early problems in communication are often related to problems with social cognition, motivation, and emotional expression. Patients who fail to respond with appropriate language or tact can experience a breakdown in communication with friends and neighbors that are unaware of the FTD diagnosis. The perception of emotional detachment can also lead others to shy away from initiating conversation with the patient. Indifference and apathy can lead to diminished speech, causing some patient needs to not be met. While these symptoms usually cannot be directly targeted in the patient, educating caregivers on better communication styles can help minimize their effects. Open-ended questions may fail to generate responses, but patients often respond better when given defined choices. Indirect repairs that

restate an understanding of what was said can lead to higher quality interactions than direct repairs that provide immediate corrective feedback. Talking down to patients using “elderspeak” (e.g., using “honey” or “sweetie”) can create resistance and negative consequences. There is some evidence in patients with AD that dementia caregivers can successfully be taught some of these communication skills, leading to fewer behavioral disturbances [43].

Patients with PPA suffer impairments in communication due to the accumulation of deficits in language abilities. Behavioral interventions are the mainstay for ameliorating the effects of these impairments. These generally fall into two categories. One approach is to attempt to maintain or improve deteriorating language skills through language therapy. Thus far, case reports suggest that abilities such as comprehension of spoken instructions and questions, production of sentences, and word retrieval may be amenable to short-term improvement using domain-specific language exercises [44]. Formal studies documenting the efficacy of these types of interventions are lacking, as is evidence that these benefits remain after the conclusion of therapy. Patients that have retained insight, are motivated to learn, and have supportive and actively involved caregivers are the best candidates to pursue these interventions. Speech-language pathologists (SLPs) that have experience working with neurodegenerative conditions can help tailor interventions to individual needs.

More commonly, patients with PPA will benefit from interventions that maximize functional communication through compensatory strategies. Although they are underutilized in PPA [45], SLPs are trained to introduce a variety of such interventions for patients with stroke and other disorders [46]. At the mild stages, SLPs may suggest adopting strategies such as self-cueing and script training to enhance conversation. In more moderate stages of the disease, augmentative and alternative communication devices (AACs)

such as communication books can be utilized to supplement speech. Electronic and computer AACs require intact learning ability, necessitating training while cognitive impairment is relatively mild. SLPs can also suggest ways for families to promote better communication with the patient. Families can be advised that speaking slowly, simply, and face-to-face facilitates greater language comprehension. Noise and other distractions should be minimized to ease understanding. Providing more time for communication, asking for clarification, and supplementing speech with gestures are other tips that will reduce a breakdown in communication.

Motor impairments

Patients with FTD spectrum disorders can present with motor deficits that complicate the management of the disease. Falls are frequent in PSP especially. Physical therapists can play an important role in intervention by assessing mobility and prescribing weighted or rolling walkers or wheelchairs as needed. Trained health aides and family members can help reduce falls. Physical therapy can also be instituted to promote passive range of motion in affected muscles, especially for the dystonia of CBS, helping to prevent contractures and maintain limber joints [47]. Environmental modifications are essential interventions to ensure patient safety and can be suggested by occupational and physical therapists. These may include instituting predictable schedules, arranging for supervision when travel is required, and reducing environmental hazards such as throw rugs and clutter.

Behavioral disturbances and neuropsychiatric impairments

Social and behavioral disturbances are the most frequent cause of distress for FTD caregivers [48]. Pharmacologic measures can sometimes reduce

positive symptoms such as disinhibition and agitation, but non-pharmacologic interventions are frequently necessary for dealing with the full scope of symptoms. Given the lack of insight commonly seen in FTD, environmental modifications and educational measures targeting the caregiver can be useful to help manage these symptoms.

Apathy and inertia. Patients lose interest and drive in undertaking previously rewarding activities (apathy), or are not able to initiate or complete actions on their own (inertia). For example, patients may give up some hobbies in favor of passively watching TV, or be unable to finish preparing a meal or brushing their teeth. Caregivers can sometimes help the patient successfully engage in life activities. One suggestion is to offer several options for activities to do together rather than leaving things up to the patient in an open-ended way. In other cases, the caregiver may need to direct the person as to what to do. For completing activities around the home, the caregiver may be able to divide a task into small, simple steps and provide guidance to help the patient finish it. For chores such as cooking that may be hazardous if not done in an appropriate way, supervision may be provided. Participating in passive activities such as watching movies with the patient can still be a source of mutual satisfaction. It should be noted that families often experience frustration when trying to find activities that will engage the patient's interest. To reduce tension and strain, they should be counseled to lower their expectations about how interested the person can be and that their lack of interest is a symptom of the illness.

Disinhibition and impulsive behaviors. Patients with bvFTD show a decreased ability to assess the social and practical consequences of their words and actions. As such, they exhibit poor decision-making and judgment. This may manifest as vulnerability to sales pitches, impulse buying, reckless driving, indiscriminate sharing of personal information,

gambling, or shoplifting. In social situations, patients can become more impulsive and violate typical norms. They may laugh inappropriately, make offensive jokes, or stand too close to strangers. Caregivers can modify the environment in order to reduce harmful consequences from these behaviors. Postal delivery can be changed to a post office box so that mail can be better supervised. Access to bank accounts and credit cards can be limited to avoid financial recklessness. Car keys can be kept away from the patient. Guns and other weapons should be removed from the house. In social contexts, caregivers can be advised to monitor the patient's contact with the public. Going to venues where the patient is already known and explaining the diagnosis to neighbors can reduce the chances of misunderstanding the patient's behavior. Families may choose to sit in more secluded areas of the theater or restaurant to minimize disruptions. Electronic devices with GPS can be used track the patient's location and prevent wandering out of sight. Cards that explain the patient's behavior as a symptom of illness can also be passed out if necessary.

Socially disruptive behaviors sometimes necessitate the involvement of clinicians. In legal settings, clinicians may be called upon as expert witnesses to assess responsibility or risk of future criminal behavior in patients. Clinicians should monitor for physically abusive or sexually inappropriate behavior towards minors. In these cases, the safety and welfare of children is paramount. Families should be advised to keep children away from patients displaying these behaviors, and these behaviors will likely necessitate placement in a different setting without children present.

Loss of empathy and sympathy. Diminished responsiveness to other people's needs and decline in social engagement is a feature of bvFTD. Patients may make hurtful comments that fail to appreciate other people's feelings. Blunted emotional and facial expression such as lack of eye

contact can cause friends and family to see the patient as cold and distant. Family members may not be thanked for attending to caregiving tasks, or the patient may stop playing with children or grandchildren. These symptoms can cause confusion and hurt in family members. Given their strong emotional and developmental needs and lack of understanding, children are especially vulnerable to being affected and may experience feelings of guilt or responsibility when they fail to receive previously available emotional warmth and encouragement. An important intervention for managing the effects of this symptom is education and support about the nature of the disease. Understanding these symptoms as a product of changes in the brain can mitigate emotional upheaval in the family. Caregiver support groups and conferences and FTD websites are often valuable resources towards this end. Well parents should take care to have open and truthful communication with their children, and to monitor their emotional states. Psychotherapy for children or other family members may be indicated. In addition, well parents can support their children by modeling healthy coping skills and finding outlets for engaging their strengths and accomplishments [49].

Perseverative and ritualistic behavior. Patients can engage in repetitive and stereotyped behaviors or compulsively engage in certain actions. Examples include repeatedly saying a phrase or story, washing the same item, walking a fixed route, collecting the same object, or rubbing a body part. The simplest response may be to advise the caregiver to tolerate the behavior, especially if it is relatively harmless. Sometimes a less distressful behavior can be substituted for the current one. For example, a laptop or portable DVD player can allow a patient to watch the same TV show over and over again without getting in the way of going to a doctor's appointment. Distraction is another method that can be used to displace the patient's attention away from a repetitive behavior or routine. If the

behavior gets in the way of important responsibilities or leads to risky situations, pharmacologic management of the symptom may be warranted.

Compulsive eating and dietary abnormalities. Patients can exhibit profound changes in eating behavior, often developing carbohydrate cravings and eating past the point of satiety. Sometimes, patients ingest inedible items or compulsively consume alcohol. These symptoms can often be very frightening for the family and lead them to institute necessary environmental modifications. Locking cabinets and refrigerators, removing unsafe foods from the home, and providing supervision during mealtimes are all steps that can be taken to minimize danger. Providing only small portions on plates can be useful. A dietitian can be consulted to strategize ways to provide appropriate nutrition while attending to safety needs. As with all behavioral symptoms of FTD, helping families to adjust expectations can be helpful. For example, some family members become very concerned with weight gain during the illness. But conflict with the patient can sometimes be reduced if some increase in food intake, and weight, is tolerated. Eating too quickly and putting too much food in their mouths can be a life-threatening symptom if it leads to choking, and this symptom can be especially dangerous in patients with FTD-ALS and dysphagia.

Aggression and agitation. Irritability, frustration, or anger may be expressed by some patients, sometimes during caregiving tasks. These behaviors cause the greatest burden for caregivers and are correlated with high levels of caregiver depression [9]. Remaining calm, avoiding arguments, and maintaining distance from the patient are strategies that can be adopted to reduce the chances of conflict. Caregivers are advised to look for specific causes for agitated behaviors, such as a medical problem or uncommunicated physical needs. Specific environmental triggers such as loud noises or social setting lead some patients to feel overwhelmed and

respond negatively. Attending to these issues can decrease problematic behaviors. New physical limitations and environmental constraints are sometimes a source of frustration for patients. For example, patients with FTD-ALS may refuse to use walkers, putting them at greater risk for injury. In these cases, the caregiver can become overburdened as well as become the target of the patient's aggression. These challenging behaviors can cause caregivers to crave respite from caregiving responsibilities.

Depression. While symptoms of depression may be seen in both bvFTD and PPA, in bvFTD, somatic factors such as decreased motivation and inertia are often dominant, with little evidence of affective symptoms such as depressed mood, poor self-esteem, or suicidality. These patients, because of their poor reasoning abilities and lack of insight, are generally poor candidates for psychotherapy. Patients with PPA are at greater risk for developing depressed mood and related symptoms [50]. This may be due to their relatively preserved insight into their cognitive and behavioral difficulties [51], combined with increasing inability to express themselves and communicate their emotional needs. Language deficits frequently lead these patients to withdraw from social interaction with peers and family members. An inability to do everyday tasks, such as reading the newspaper and answering the telephone, sometimes leads to feelings of worthlessness. Gradual difficulty in participating in life activities can take an emotional toll on patients with PPA. Introducing new hobbies that do not require language, such as doing puzzles or painting, can help keep patients engaged. Counseling may help some patients come to terms with their loss of identity. Creative arts therapies involving dance or music can promote relaxation. Case studies and small trials suggest that visual art therapy can be harnessed to engage attention and improve neuropsychiatric symptoms and self-esteem [52].

Non-pharmacologic interventions have been shown to be effective in managing some of the behavioral symptoms of dementia both in institutional settings and via caregiver delivery at home [53]. Day programs are one example of an intervention that is delivered in an institutional setting. These programs benefit patients by providing structure and stimulating and meaningful activities, such as gardening and exercise. They also help caregivers by providing much-needed respite and leading to reduced stress. Despite their benefits, FTD patients often do not fit the limits of care of these programs [54]. For example, staff are not trained to deal with socially disruptive behaviors, and are ill-prepared for the changes in eating behavior associated with bvFTD. Preliminary findings in a recently established FTD-specific day program include increases in facial expression and initiation of participation in activities and decreases in inappropriate behaviors [54]. Further research into these types of programs will help clarify the activities most beneficial for FTD patients.

A large part of managing FTD inevitably falls on the shoulders of the caregiver, often the spouse or child of the patient. Largely owing to the centrality of behavioral symptoms, FTD caregivers experience particularly high burden and strain compared with caregivers of other dementias [48, 55]. The young age of onset in FTD often leads to disruption in family life, leading to feelings of loss and anxiety for children. Financial strain is likely to result when a main provider for the family can no longer work. Social isolation and depression are common developments amongst FTD caregivers, especially given the stigmatization they may feel due to a lack of societal awareness of the disease [48]. These factors all add to the nuances involved in the practical management of FTD.

Identifying resources to help caregivers deal with the manifold consequences of this disease is an integral part of the clinician's responsibility (see [Table 17.2](#)). Education and information are most

effective when paired with more concrete steps to deal with behavioral symptoms. Referrals to occupational therapists, geriatric nurses, and other clinicians with experience in teaching behavioral modification techniques can help caregivers learn practical skills to better manage distressing behaviors. An example of such a technique is the Advanced Caregiver Training (ACT) model. In this model, dementia caregivers are taught how to identify triggers of patient behavior by monitoring medical conditions, environmental factors, and caregiver communication style [56]. Applying ACT and similar methods can reduce the burden of care as well as caregiver upset [56]. In addition to resources that can help with the practical management of behaviors, caregivers should also be introduced to resources to help them better manage their own mental health. Programs that target dementia caregiver emotional coping strategies can reduce depressive symptoms and psychological distress [57], preventing a breakdown in care and eventually leading to improved quality of life for patients [58]. Clinicians can also recommend psychiatric treatment for some caregivers whom they think would benefit.

Table 17.2 Multidisciplinary management and coordination of care at different stages of FTD

Aspect of multidisciplinary management	Early stage, mild impairment	Middle stage, moderate impairment	Advanced stage, severe impairment
Physician responsibilities	Diagnosis; discussion of diagnosis and course of disease; assessment of degree of assistance needed (e.g., home health aides); assessment of burdensome	Continued assessment of symptoms; assessment of degree of assistance needed (e.g., possible out-	Assessment of degree of assistance needed (e.g., possible out-of-home-placement or hospice

	symptoms and prescribing medications to manage them if necessary; assessment for genetic testing and referral to a genetic counselor if warranted	of-home-placement); discussion of medication efficacy, side effects, and dosing adjustments as needed	referral); discussion of genetic implications of neuropathologic findings after autopsy
Programmatic patient support	Consultations with cognitive rehabilitation professionals, physical therapists, speech therapists, and/or occupational therapists to enhance life participation and maintain functional abilities; caregiver assistance and supervision to complete basic activities of daily living; day programs for meaningful activity; home health aides to help with patient self-care tasks and physical and safety needs; referrals to residential facilities, palliative care, and hospice when appropriate		
Caregiver support	Introduction to educational materials and supportive local, national, and online resources; home health aide or companion to assist caregiver; day programs to provide caregiver with respite; meetings with support groups; emotion-focused coping strategies for grief and loss, and bereavement support		
Advance care planning	Identification of healthcare proxy; completion of power-of-attorney; consultation with social worker regarding benefit eligibility	Consultation with a social worker; identification of suitable hospice and/or residential care facilities	Discussions to help family and patient plan for a peaceful death; logistic and financial planning for death

Most recommendations for caregiver support are drawn from clinical experience and research with dementia caregivers in general, as research studies specific to interventions for FTD caregivers have been limited to date. One study has shown that FTD caregivers can successfully be taught to appraise stressful situations and implement appropriate strategies for responding, leading to reduced caregiver burden and reactions to challenging behaviors [59]. Another study has linked emotion-focused coping strategies to differences in mental health [60]. There is also preliminary evidence that FTD caregivers can benefit from directly cultivating positive affect through such methods as mindfulness, expressions of gratitude, and altruistic behavior [61]. FTD caregivers report information about the disease, psychosocial support through trained personnel, and financial support as the most helpful interventions [9]. Given their household responsibilities, caregivers commonly have little time to attend face-to-face support groups. Online websites and videoconferencing interventions have recently been established that will likely prove to be of particular benefit [54]. These findings can guide the development of better supportive services for FTD caregivers in the future.

Management at advanced stages

In the later stages of FTD, patients exhibit a decline in goal-directed behaviors. Fewer socially inappropriate and problematic behaviors may be seen, and the prevailing symptoms are often apathy and inertia [62]. Frequently, patients lose the ability or initiative to communicate needs. Patients with PPA and language disturbances can progress to the point of mutism. Functionally, patients have difficulty independently completing basic activities of daily living [5]. At this point, management efforts shift

from an emphasis on facilitating life participation and managing distressing behaviors to helping with self-care tasks and physical needs. Preparing and eating food, using the toilet, bathing, and dressing may all require the help of a caregiver or 24-hour home care aide. Increased supervision is necessary to ensure patient safety throughout the day.

Caregivers are often overwhelmed with the level of care the patient increasingly requires at this stage. Given the early age of onset, many are still employed or have child-rearing responsibilities, and lack the capacity to provide safe and continuous care. At this point, or earlier if the patient has needs or symptoms that are difficult to manage in the home, families may consider placing the patient in a residential care program. This can be a difficult process, both from a practical standpoint as well as an emotional one. FTD caregivers often experience frustration in finding care facilities that accept younger patients with a history of inappropriate social behavior or agitation. Many residential facilities are set up to accept older adults with an AD model of disease progression. Social workers can help find an appropriate facility given the unique features of FTD. Emotionally, families sometimes struggle with the decision to let go of their loved one and to see them with much older participants [7]. Once the patient is placed, caregivers can experience a wide range of emotions, including sadness, guilt, and relief. Clinicians can help by educating them about the transition process and setting expectations for the changes that will come and the feelings that may develop [7]. They can also continue an active role in treatment by establishing a relationship with medical staff at the residential care facility.

Whether at a facility or at home, patients will decline in the ability to handle personal care. In the end stages of FTD, patients can become bedridden and completely dependent on others [5]. They become less interested in eating and commonly have difficulty chewing and swallowing,

leading to weight loss [63]. Incontinence and somnolence are common developments [63]. There is frequently little or no meaningful interpersonal communication. At this stage, referrals to palliative care and hospice are warranted [63]. Hospice teams can evaluate the patient's condition to maintain basic quality of life, provide comfort, and relieve suffering to the extent possible. During their last days, patients become prone to infections. Complications of late-stage symptoms such as aspiration pneumonia, choking, and respiratory weakness commonly lead to death [63].

Once the patient has died, if a brain donation has been arranged beforehand, the family should be contacted to discuss the findings from the neuropathology report. An autopsy-confirmed case of FTD can lead to questions about genetic implications for family members [7]; therefore, clinicians should be able to discuss the consequences of genetic testing or refer families to a genetic counselor (see [Chapter 12](#)). Clinicians should also be aware that neuropathologic findings may diverge from the clinical diagnosis. This can sometimes lead to confusion in family members, who may need to be educated and counseled about clinical–pathologic discrepancies.

Conclusions

FTD is a multifaceted and heterogeneous illness that can include fluctuating cognitive, behavioral, language, and motor symptoms. These symptoms affect the quality of life of both the patient and family and caregiver, often necessitating a variety of interventions at different periods throughout the disease course. The multidisciplinary clinic therefore presents an ideal model for the practical management of the disease. While formal studies incorporating this model have not been tested in FTD, patients with related

illnesses, such as ALS, utilizing such clinics benefit from greater quality of life [64]. FTD caregivers highly desire the one-stop, all-inclusive centers for information and management that a multidisciplinary clinic can provide [9]. Multidisciplinary teams for FTD can integrate different elements of care and management including behavioral and cognitive assessment, pharmacologic treatment, caregiver training, and identification of supportive local resources. Behavioral neurologists, geriatric psychiatrists, neuropsychologists, social workers, genetic counselors, physical and occupational therapists, speech-language pathologists, and palliative care nurses can all play a role in the comprehensive management of FTD.

References

1. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. *Archives of Neurology* 2007;**64**(6):830–5.
2. Chow TW, Pio FJ, Rockwood K. An international needs assessment of caregivers for frontotemporal dementia. *The Canadian Journal of Neurological Sciences. Le Journal Canadien des Sciences Neurologiques* 2011;**38**(5):753–7.
3. Rascofsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain: A Journal of Neurology* 2011;**134**(Pt 9):2456–77.
4. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, *et al.* Classification of primary progressive aphasia and its variants. *Neurology* 2011;**76**(11):1006–14.
5. Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and

disease progression in frontotemporal dementia. *Neurology* 2010;**74**(20):1591–7.

6. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *The Journal of Clinical Psychiatry* 2011;**72**(2):126–33.

7. Wylie MA, Shnall A, Onyike CU, Huey ED. Management of frontotemporal dementia in mental health and multidisciplinary settings. *International Review of Psychiatry* 2013;**25**(2):230–6.

8. Mesulam MM, Wieneke C, Thompson C, Rogalski E, Weintraub S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain: A Journal of Neurology* 2012;**135**(Pt 5):1537–53.

9. Diehl-Schmid J, Schmidt EM, Nunnemann S, Riedl L, Kurz A, Forstl H, *et al.* Caregiver burden and needs in frontotemporal dementia. *Journal of Geriatric Psychiatry and Neurology* 2013;**26**(4):221–9.

10. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. *International Review of Psychiatry* 2013;**25**(2):130–7.

11. Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. *Neurology* 2003;**61**(3):349–54.

12. Borroni B, Grassi M, Archetti S, Papetti A, Del Bo R, Bonvicini C, *et al.* Genetic background predicts poor prognosis in frontotemporal lobar degeneration. *Neuro-degenerative Diseases* 2011;**8**(5):289–95.

13. Le Rhun E, Richard F, Pasquier F. Natural history of primary progressive aphasia. *Neurology* 2005;**65**(6):887–91.

14. Borroni B, Benussi A, Cosseddu M, Archetti S, Padovani A. Cerebrospinal fluid tau levels predict prognosis in non-inherited frontotemporal dementia.

Neuro-degenerative Diseases 2014;**13**(4):224–9.

15. Salmon E, Perani D, Collette F, Feyers D, Kalbe E, Holthoff V, *et al.* A comparison of unawareness in frontotemporal dementia and Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 2008;**79**(2):176–9.

16. The Association for Frontotemporal Degeneration [cited December 2013]. Available from: www.theaftd.org.

17. Jicha GA. Medical management of frontotemporal dementias: the importance of the caregiver in symptom assessment and guidance of treatment strategies. *Journal of Molecular Neuroscience: MN* 2011;**45**(3):713–23.

18. Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, *et al.* Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain: A Journal of Neurology* 2008;**131**(Pt 11):2957–68.

19. Sapolsky D, Bakkour A, Negreira A, Nalipinski P, Weintraub S, Mesulam MM, *et al.* Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia. *Neurology* 2010;**75**(4):358–66.

20. Dickerson BC. Quantitating severity and progression in primary progressive aphasia. *Journal of Molecular Neuroscience: MN* 2011;**45**(3):618–28.

21. de Simone V, Kaplan L, Patronas N, Wassermann EM, Grafman J. Driving abilities in frontotemporal dementia patients. *Dementia and Geriatric Cognitive Disorders* 2007;**23**(1):1–7.

22. Manoochehri M, Huey ED. Diagnosis and management of behavioral issues in frontotemporal dementia. *Current Neurology and Neuroscience Reports* 2012;**12**(5):528–36.

23. Huey ED, Putnam KT, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* 2006;**66**(1):17–22.

24. O'Brien JT, Burns A, BAP Dementia Consensus Group. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2011;**25**(8):997–1019.

25. Parashos SA, Wielinski CL, Giladi N, Gurevich T. Falls in Parkinson disease: analysis of a large cross-sectional cohort. *Journal of Parkinson's Disease* 2013;**3**(4):515–22.

26. Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, *et al.* Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA: The Journal of the American Medical Association* 2011;**306**(12):1359–69.

27. Steinberg M, Lyketsos CG. Atypical antipsychotic use in patients with dementia: managing safety concerns. *The American Journal of Psychiatry* 2012;**169**(9):900–6.

28. Devanand DP, Schultz SK, Sultzer DL. Discontinuation of risperidone in Alzheimer's disease. *The New England Journal of Medicine* 2013;**368**(2):187–8.

29. Lopez-Pousa S, Calvo-Perxas L, Lejarreta S, Cullell M, Melendez R, Hernandez E, *et al.* Use of antidementia drugs in frontotemporal lobar degeneration. *American Journal of Alzheimer's Disease and Other Dementias* 2012;**27**(4):260–6.

30. Kerchner GA, Tartaglia MC, Boxer A. Abhorring the vacuum: use of Alzheimer's disease medications in frontotemporal dementia. *Expert Review of Neurotherapeutics* 2011;**11**(5):709–17.

31. Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, *et al.* Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*

Neurology 2013;**12**(2):149–56.

32. Vercelletto M, Boutoleau-Bretonniere C, Volteau C, Puel M, Auriacombe S, Sarazin M, *et al.* Memantine in behavioral variant frontotemporal dementia: negative results. *Journal of Alzheimer's Disease: JAD* 2011;**23**(4):749–59.

33. van Balken I, Litvan I. Current and future therapeutic approaches in progressive supranuclear palsy. *Handbook of Clinical Neurology* 2008;**89**:493–508.

34. Boeve BF, Josephs KA, Drubach DA. Current and future management of the corticobasal syndrome and corticobasal degeneration. *Handbook of Clinical Neurology* 2008;**89**:533–48.

35. Constantinescu R, Richard I, Kurlan R. Levodopa responsiveness in disorders with parkinsonism: a review of the literature. *Movement Disorders: Official Journal of the Movement Disorder Society* 2007;**22**(15):2141–8; quiz 295.

36. Diniz BS, Machado-Vieira R, Forlenza OV. Lithium and neuroprotection: translational evidence and implications for the treatment of neuropsychiatric disorders. *Neuropsychiatric Disease and Treatment* 2013;**9**:493–500.

37. ClinicalTrials.gov: A Pilot Trial of Lithium in Subjects With Progressive Supranuclear Palsy or Corticobasal Degeneration [updated June 18, 2010; cited December 12, 2013]. Available from:
<https://clinicaltrials.gov/show/NCT00703677>.

38. ClinicalTrials.gov: Effects of Tolcapone on Frontotemporal Dementia [updated October 18, 2011; cited December 12, 2013]. Available from:
<https://www.clinicaltrials.gov/ct2/show/NCT00604591>.

39. Finger EC. New potential therapeutic approaches in frontotemporal dementia: oxytocin, vasopressin, and social cognition. *Journal of Molecular Neuroscience: MN* 2011;**45**(3):696–701.

40. Jesso S, Morlog D, Ross S, Pell MD, Pasternak SH, Mitchell DG, *et al.* The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. *Brain: A Journal of Neurology* 2011;**134**(Pt 9):2493–501.

41 ClinicalTrials.gov: Safety Study of Intranasal Oxytocin in Frontotemporal Dementia [cited May 2012]. Available from:
<https://clinicaltrials.gov/ct2/show/NCT01386333>.

42. Achi EY, Rudnicki SA. ALS and frontotemporal dysfunction: a review. *Neurology Research International* 2012;**2012**:806306.

43. Buchanan JA, Christenson A, Houlihan D, Ostrom C. The role of behavior analysis in the rehabilitation of persons with dementia. *Behavior Therapy* 2011;**42**(1):9–21.

44. Croot K, Nickels L, Laurence F, Manning M. Impairment- and activity/participation-directed interventions in progressive language impairment: clinical and theoretical issues. *Aphasiology* 2009;**23**(2):125–60.

45. Taylor C, Kingma RM, Croot K, Nickels L. Speech pathology services for primary progressive aphasia: exploring an emerging area of practice. *Aphasiology* 2009;**23**(2):161–74.

46. Khayum B, Wieneke C, Rogalski E, Robinson J, O'Hara M. Thinking outside the stroke: treating primary progressive aphasia (PPA). *Perspectives on Gerontology* 2012;**17**(2):37–49.

47. Reich SG, Grill SE. Corticobasal degeneration. *Current Treatment Options in Neurology* 2009;**11**(3):179–85.

48. Nunnemann S, Kurz A, Leucht S, Diehl-Schmid J. Caregivers of patients with frontotemporal lobar degeneration: a review of burden, problems, needs, and interventions. *International Psychogeriatrics/IPA* 2012;**24**(9):1368–86.

-
- 49.** Denny SS, Morhardt D, Gaul JE, Lester P, Andersen G, Higgins PJ, *et al.* Caring for children of parents with frontotemporal degeneration: a report of the AFTD Task Force on Families With Children. *American Journal of Alzheimer's Disease and Other Dementias* 2012;**27**(8):568–78.
-
- 50.** Banks SJ, Weintraub S. Neuropsychiatric symptoms in behavioral variant frontotemporal dementia and primary progressive aphasia. *Journal of Geriatric Psychiatry and Neurology* 2008;**21**(2):133–41.
-
- 51.** Banks SJ, Weintraub S. Generalized and symptom-specific insight in behavioral variant frontotemporal dementia and primary progressive aphasia. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2009;**21**(3):299–306.
-
- 52.** Chancellor B, Duncan A, Chatterjee A. Art therapy for Alzheimer's disease and other dementias. *Journal of Alzheimer's Disease: JAD* 2014;**39**(1):1–11.
-
- 53.** Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. *The American Journal of Psychiatry* 2012;**169**(9):946–53.
-
- 54.** Shnall A, Agate A, Grinberg A, Huijbregts M, Nguyen MQ, Chow TW. Development of supportive services for frontotemporal dementias through community engagement. *International Review of Psychiatry* 2013;**25**(2):246–52.
-
- 55.** Riedijk SR, De Vugt ME, Duivenvoorden HJ, Niermeijer MF, Van Swieten JC, Verhey FR, *et al.* Caregiver burden, health-related quality of life and coping in dementia caregivers: a comparison of frontotemporal dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders* 2006;**22**(5–6):405–12.
-
- 56.** Gitlin LN, Winter L, Dennis MP, Hodgson N, Hauck WW. Targeting and managing behavioral symptoms in individuals with dementia: a randomized trial of a nonpharmacological intervention. *Journal of the American Geriatrics Society* 2010;**58**(8):1465–74.
-

57. Selwood A, Johnston K, Katona C, Lyketsos C, Livingston G. Systematic review of the effect of psychological interventions on family caregivers of people with dementia. *Journal of Affective Disorders* 2007;**101**(1–3):75–89.

58. Cooper C, Mukadam N, Katona C, Lyketsos CG, Ames D, Rabins P, *et al.* Systematic review of the effectiveness of non-pharmacological interventions to improve quality of life of people with dementia. *International Psychogeriatrics/IPA* 2012;**24**(6):856–70.

59. Mioshi E, McKinnon C, Savage S, O'Connor CM, Hodges JR. Improving burden and coping skills in frontotemporal dementia caregivers : a pilot study. *Alzheimer Disease and Associated Disorders* 2013;**27**(1):84–6.

60. Wong CC, Wallhagen MI. Family caregivers of individuals with frontotemporal dementia: examining the relationship between coping and caregiver physical and mental health. *Journal of Gerontological Nursing* 2014;**40**(1):30–40.

61. Dowling GA, Merrilees J, Mastick J, Chang VY, Hubbard E, Moskowitz JT. Life enhancing activities for family caregivers of people with frontotemporal dementia. *Alzheimer Disease and Associated Disorders* 2014;**28**(2):175–81.

62. Chow TW, Fridhandler JD, Binns MA, Lee A, Merrilees J, Rosen HJ, *et al.* Trajectories of behavioral disturbance in dementia. *Journal of Alzheimer's Disease: JAD* 2012;**31**(1):143–9.

63. Gallagher MM, McLean A, Wilson R. *Discussion of Hospice and End-of-Life Symptoms in FTD*. Phoenix, Arizona: Hospice of the Valley, 2011.

64. Van den Berg JP, Kalmijn S, Lindeman E, Veldink JH, de Visser M, Van der Graaff MM, *et al.* Multidisciplinary ALS care improves quality of life in patients with ALS. *Neurology* 2005;**65**(8):1264–7.

Chapter 18

Pharmacologic therapy for FTD and related disorders



Current options and future strategies

Richard M. Tsai and Adam L. Boxer

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Introduction

Currently there are no US Food and Drug Administration (FDA)-approved therapies for frontotemporal dementia (FTD). Some medications are used off-label for symptomatic management; however, there is minimal evidence for efficacy to support their use. Such therapies rely on modulation of neurotransmitter levels and do not target the underlying pathophysiology of FTD. The limited number of cases of FTD, heterogeneous presentations of FTD, and diverse pathology has historically made it difficult to conduct adequately powered placebo-controlled clinical trials. Most studies of medications have grouped disparate clinical syndromes together and did not attempt to stratify by underlying pathology.

Fortunately there have been remarkable advancements in the understanding of frontotemporal lobar degeneration (FTLD) pathophysiology, genetics, and neuropathology recently. New biomarkers, and new cellular and animal models have been developed. Advances in treatment development for Alzheimer's disease (AD), which shares some pathogenic molecules with FTD, particularly tau, are likely to inform FTD drug developments, and potentially provide disease-modifying therapies in FTD. Finally, new molecular imaging techniques including tau positron emission tomography (PET) scanning will greatly improve the feasibility of carrying out trials in well-defined FTD syndromes.

This chapter will review the evidence for currently available pharmacologic therapies for FTD and its related disorders. In addition it will discuss potential therapy targets for disease-modifying treatment, pharmacologic therapies in various stages of development, as well as models that may accelerate therapy discovery. The chapter will conclude with suggestions for collaboration with industry partners, clinical trials design, and regulatory considerations.

Neurotransmitter-based symptomatic treatments

Most current medications for FTD were developed for use in psychiatric disorders or AD, and are not indicated for FTD treatment, but are used in desperation to try to manage the behavioral symptoms of FTD. These agents work by modulating the levels or downstream effects of various central nervous system (CNS) neurotransmitters, strategies that are effective in Parkinson's disease and Alzheimer's disease. Previous research has implicated alterations in cholinergic, serotonergic, dopaminergic,

noradrenergic, and glutamatergic systems in FTD [1]. However, there have been few high-quality clinical studies of therapeutic agents that target these alterations. Most of the available evidence is limited to small case series or open label clinical trials. In addition, there are examples of initially promising therapies for FTD identified in open label studies that have not stood up to the rigors of randomized, double-blind, placebo-controlled trials, underscoring the need to interpret the vast majority of previous clinical therapeutic research in FTD with extreme caution. With these caveats in mind, we review the previous literature on symptomatic therapies for FTD below.

Antidepressants

The serotonergic system has been suggested to mediate behaviors such as impulsivity, aggression, and disinhibition [2]. These behaviors are also commonly seen in behavioral variant (bvFTD) patients. Neuropathologic analyses have shown FTD patients to have a dysfunctional serotonergic system, with reduction of 5-HT1 and 5-HT2A serotonin receptors in orbital frontal, cingulate, medial frontal, and temporal regions [3, 4]. Another study also demonstrated a 40% loss of neurons in the serotonergic raphe nuclei [5]. Selective serotonin reuptake inhibitors (SSRIs) are attractive agents for use in FTD patients as they increase serotonin levels, and have historically been successful in treating clinical symptoms in psychiatric patients that resemble some of the problematic FTD behaviors. As shown in [Table 18.1](#), SSRIs such as citalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, and clomipramine have all been described to be beneficial for managing FTD behaviors in small open label clinical trials or case series [6–14]. Unfortunately, as is often the case, efficacy in small preliminary studies has not been replicated in randomized placebo-controlled clinical trials.

Paroxetine showed significant behavioral improvements in two open label trials but failed to demonstrate improvements in a subsequent six-week, double-blind, placebo-controlled crossover trial [15]. The only medication with serotonergic activity with proven efficacy in a small randomized, double-blind, placebo-controlled trial was trazodone, which demonstrated improvements in Neuropsychiatric Inventory (NPI) scores 12 weeks after treatment [16]. Most clinicians believe that antidepressants may help to manage various behavioral symptoms in FTD patients, but with most evidence coming from open label trials or case series, the evidence to support this opinion is mainly anecdotal.

Table 18.1 Antidepressants in FTD

Drug	Study design	n	Dx	Citation	End point
Citalopram	6 week open label, no placebo	15	FTD	6	Improved NPI, FBI
Fluoxetine	3 month open label, no placebo	5	FTD	7	Improved disinhibition, depressive symptom, carbohydrate craving, and compulsions
Paroxetine	Case series	11	FTD/nfvPPA/svPPA	8	Improved repetitive behavior
	14 month open label, randomized, no placebo,	16	FTD	9	Improved NPI, RSS

	compared to piracetam				
	6 week, double- blind, placebo- controlled, crossover	10	FTD	15	No significant difference in NPI, C Decrease some cognitive tasks
Sertraline	3 month open label, no placebo (fluoxetine and paroxetine also used)	5	FTD	7	Improved disinhibiti depressiv symptom carbohydr craving, a compulsi
	6 month open label, no placebo, compared with AD patients	18	FTD	10	Decrease stereotyp movemen
	Case report	1	FTD–ALS	11	Improved appropria sexual behavior
	2 and 4 weeks open label	4	svPPA	12	Improved NPI
Fluvoxamine	12 week open label, no placebo	16	FTD, svPPA	13	Improved NPI

Trazodone	12 week randomized, placebo- controlled, double- blind crossover	26	FTD	16	Improved NPI
Clomipramine	Case series	3	bvFTD	14	Improved behavior

NPI = Neuropsychiatric Inventory, FBI = Frontal Behavioral Inventory, nvPPA = non-fluent variant primary progressive aphasia, svPPA = semantic variant primary progressive aphasia, RSS = Relative Stress Scale, CBI = Cambridge Behavioural Inventory, ALS = amyotrophic lateral sclerosis.

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors have long been a mainstay of AD symptomatic treatment, based on the loss of cholinergic neurons from the nucleus basalis of Meynert. Perhaps because of their success in AD, acetylcholinesterase inhibitors have been studied more rigorously than other off-label treatments in FTD ([Table 18.2](#)). However, as reviewed by Huey *et al.* in 2006, in contrast to AD, the cholinergic system in FTD patients is relatively spared from pathology [[17](#)]. Clinical trials for the three most commonly used acetylcholinesterase inhibitors have produced disappointing results, although none were large enough or designed to allow for a true efficacy determination. A 12-month open label study of rivastigmine dosed 3–9 mg/day showed some improvements in NPI score but did not prevent cognitive deterioration as measured by the Mini-Mental State Examination(MMSE) [[18](#)]. A second study investigated galantamine in 36 bvFTD and primary progressive aphasia (PPA) patients. All patients were treated in an open label fashion for 18 weeks followed by a randomized,

double-blind, placebo-controlled withdrawal period for 8 weeks. No significant differences were found in the bvFTD group, while language function remained stable in some of the treated PPA group compared with placebo, who likely had the logopenic form of PPA caused by underlying Alzheimer's pathology [19]. Donepezil, perhaps the most widely used cholinesterase inhibitor, was studied in a 6-month, open label study in 24 bvFTD patients. The donepezil-treated group had greater worsening on the FTD inventory, and four of the treated patients had worsening behavior. Discontinuation of donepezil led to an abatement of behavioral symptoms, which was replicated in a more recent discontinuation trial of donepezil in FTD patients conducted in Japan [20, 21]. Currently, the evidence suggests cholinesterase inhibitors are not effective treatments in FTD patients and may exacerbate behavioral symptoms. Routine use is not recommended.

Table 18.2 Acetylcholinesterase inhibitors in FTD

Drug	Study design	N	Dx	Citation	End point
Donepezil	6 month, non-randomized open label	24	bvFTD	20	Worsening behavioral symptoms
	2 week discontinuation study	23	FTD	21	Improved NPI and Zarit Burden Interview
Galantamine	18 week open label followed by 8 week randomized, double-blinded	36	bvFTD, PPA	19	No significant changes seen in behavior, non-significant stabilization of language scores for

					PPA group
Rivastigmine	12 month open label, compared with control group	20	FTD	18	Improved NPI and other behavioral scores, no improvements in cognition

Antipsychotics and dopaminergic therapies

The dopaminergic system is a potential therapeutic target for FTD but poses an interesting treatment paradox. Patients with frontotemporal dementia with parkinsonism-17 (FTDP-17), a rare form of autosomal dominant FTD usually due to *MAPT* or *GRN* mutations, with symptoms of parkinsonism and FTD, have evidence of dopaminergic system dysfunction. Imaging studies such as PET and single-photon emission computed tomography (SPECT) have shown decreased presynaptic dopamine transporter binding in the striatum of FTD patients and decreased postsynaptic dopamine receptor binding in FTDP-17 patients respectively [22, 23]. Dopamine reduction in the striatum of FTD patients has also been demonstrated [24]. However, behavioral symptoms in FTD can be similar to symptoms in schizophrenia, especially in agitation and disinhibition, which are thought to be due to increased dopaminergic activity. Although it should be noted that most dopaminergic abnormalities in schizophrenia are thought to be attributed to the cortical as opposed to striatal dopaminergic system, antipsychotics with dopamine receptor antagonistic properties have successfully treated such symptoms in psychiatric patients. Thus despite the contrary evidence described above, both dopamine blockade and augmentation therapies have been evaluated in FTD patients, as listed in [Tables 18.3](#) and [18.4](#).

Table 18.3 Antipsychotics in FTD

Drug	Study design	N	Dx	Citation	End point
Quetiapine	Case series	3	FTD/nfvPPA/svPPA	8	Imp in a
	Crossover with dextroamphetamine, double-blind	8	bvFTD	29	No sig cha NP
Risperidone	Case report	1	Pick's	25	Sta of c fun
	Case series	3	FTD/nfvPPA/svPPA	8	1/3 syn agit res
Aripiprazole	Case report	1	FTD	26	Imp in c syn
	Case report	1	FTD	27	Imp in s inap beh
Olanzapine	24 month open label	17	FTD	28	Imp NP

Table 18.4 Dopaminergic agents in FTD

Drug	Study design	N	Dx	Citation	End point
Selegiline	Case series	3	FTD	31	Improved behavior

Bromocriptine	14 weeks, double-blind, placebo- controlled, crossover	6	PPA	33	No overall improvements
Methylphenidate	2 weeks, double-blind, placebo- controlled, crossover	8	FTD	32	Decreased risk-taking behavior
Dextroamphetamine	8 weeks, randomized, crossover with quetiapine, double-blind	8	bvFTD	29	Improved NPI

Evidence for the use of antipsychotics in FTD patients comes mainly from anecdotal case reports and series. Risperidone, quetiapine, and aripiprazole have been suggested to mitigate behavioral disturbances [8, 25–27]. A 24-month open label trial evaluated olanzapine in five groups of patients with various dementia diagnoses. Of the 17 patients with FTD, improvements in delusions, NPI scores, and caregiver stress were observed. Other groups with diagnoses of Lewy body dementia, vascular dementia, and Parkinson's disease dementia also experienced significant behavioral improvements [28]. In a small, double-blind, crossover study with dextroamphetamine and quetiapine involving eight FTD patients with behavioral symptoms, no difference in NPI was shown between baseline and quetiapine treatment [29]. Currently, the evidence for antipsychotic use in FTD is limited, and use carries the risk of extrapyramidal side effects, to which FTD patients are particularly vulnerable [30]. In addition, the FDA recently determined the use of atypical antipsychotics for behavioral

symptoms treatment of dementia to be associated with higher mortality than placebo, related to cardiac or infectious events, and issued a black box warning for all antipsychotics.

With the dopamine deficiencies described above, medications that augment dopamine levels or signal transduction have also been tested in FTD patients. A small series of three FTD patients evaluated the monoamine oxidase (MAO)-B inhibitor selegiline and reported improvements in NPI scores [31]. Similar results were shown in a small, randomized, double-blind crossover study in eight FTD patients using dextroamphetamine along with quetiapine, which is thought to augment dopamine levels by preventing reuptake and inducing release of dopamine [29]. Another double-blind, placebo-controlled, crossover study using methylphenidate, a dopamine and norepinephrine reuptake inhibitor, in eight FTD patients demonstrated improvements in risk-taking behaviour [32]. Six PPA patients of unspecified variant were enrolled in a double-blind, placebo-controlled, crossover trial using bromocriptine, a dopamine agonist. Mild slowing of language deterioration was detected but bromocriptine did not appear to significantly alter disease course [33]. In summary, while a variety of dopamine-modulating therapeutics have shown potentially promising preliminary results in FTD, rigorous placebo-controlled studies should be performed to determine their true safety and efficacy. Safety is a particular concern for these drugs in light of their potential adverse effects such as increased behavioral disturbances, risk-taking behavior, hallucinations; symptoms that have been observed in patients receiving dopamine replacement therapy for Parkinson's disease.

Anti-epileptics

Anti-epileptic (anticonvulsant) agents have been used as mood stabilizers for manic behaviors, but none have been studied rigorously in the treatment of FTD. Currently there are case reports and case series, as shown in [Table 18.5](#), that report experiences with such medications in FTD. The choice of anti-epileptics has typically been those with mood stabilizing effects such as carbamazepine and valproic acid, with reported improvements in behavior. [8, 34] Topiramate is an anti-epileptic with a migraine treatment indication and mood stabilizing effects and has been incorporated into some weight loss drugs based on a known propensity to cause anorexia. Interestingly, in several case reports it has been shown to reduce hyperorality in FTD patients but no placebo-controlled trials have been done [35–38].

Table 18.5 Anti-epileptics in FTD

Drug	Study design	N	Dx	Citation	End point
Carbamazepine	Case report	1	FTD	34	Reduced inappropriate sexual behavior
Topiramate	Case report	1	FTD	35	Reduced alcohol abuse
	Case report	1	FTD	36	Improvement in abnormal eating
	Case report	1	bvFTD	37	Improvement in abnormal eating
	Case series	3	FTD	38	Improvement in

					compulsive eating
Valproic acid	Case series	3	FTD/nfvPPA/svPPA	8	3/3 showed improvement in agitation

Memantine

Memantine is a (*N*-methyl D-aspartate) NMDA receptor antagonist that is indicated for the treatment of moderate to severe AD. Previously, a randomized, double-blind, placebo-controlled trial of 252 patients with moderate to severe AD demonstrated improvements in activities of daily living, cognition, and clinician impression on memantine compared with placebo [39]. Subsequently a randomized, double-blind, placebo-controlled clinical trial of 404 moderate to severe patients already on donepezil showed that addition of memantine resulted in improvements in cognition, activities of daily living, global outcome, and behavior symptoms [40]. Although the underlying pathology and neurotransmitter changes are different in AD compared with FTD, the NMDA receptor is thought to play a role in neurologic dysfunction due to range of different neurologic disorders. Excitotoxicity via overactivation of NMDA receptors by glutamate may be a final common pathway responsible for neuronal death. Whereas one small open label study demonstrated no effects of memantine in bvFTD [41], a small case series and a phase IV open label memantine study suggested improvements in behavioral symptoms as measured by the NPI [42–44]. The efficacy of memantine was further tested in two rigorous randomized, placebo-controlled clinical trials, one 52 weeks and one 26 weeks (Table 18.6) [45, 46]. Although both did not enroll the number of patients originally planned, both failed to demonstrate significant benefits on the NPI or Clinical Global Impression of Change. In addition, memantine

treatment was associated with worse performance on a number of cognitive tests [46]. These studies provide fairly strong evidence that memantine is not an effective treatment for FTD. Experience with memantine in FTD underscores the limitations of attempting to extrapolate the efficacy of drugs for FTD based on placebo-controlled trials in AD and other disorders, even when there is a strong scientific rationale for use of the drug in FTD.

Table 18.6 NMDA antagonist in FTD

Drug	Study design	n	Dx	Citation	End poin
Memantine	3 month case series	3	bvFTD	43	Improver in NPI
	6 month open label, uncontrolled	16	bvFTD	41	No chang NPI or FI overall decline in cognition
	26 week open label	43	bvFTD/nfvPPA/svPPA	44	Transient improver in NPI in FTD grou FTD and svPPA declined c cognitive behavioral stable on UPDRS. nfvPPA w stable on ADAS-co NPI, and TFLS but

				declined c UPDRS
12 month, randomized, double- blind, controlled	49	bvFTD	45	No signific changes except FE was mildly lower in treatment arm
26 weeks randomized, parallel group, double- blind, placebo- controlled	81	bvFTD/svPPA	46	No effect NPI, CGI

UPDRS = Unified Parkinson's Disease Rating Scale, ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive, TFLS = Texas Functional Living Scale, CGIC = Clinical Global Impression of Change.

Parkinsonism treatment

A substantial portion of FTD patients also present with parkinsonism. FTDP-17 refers to autosomal dominantly inherited FTD associated with mutations in the tau (*MAPT*) or progranulin (*GRN*) genes and also frequently associated with parkinsonism. Moreover the disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) which are defined by atypical parkinsonism, typically with substantial rigidity but infrequent tremor or levodopa response, overlap both clinically and neuropathologically with FTD. FTD patients with parkinsonism typically do not respond to dopaminergic therapy such as levodopa/carbidopa, although

a few cases of potential benefit have been reported [8]. When significant parkinsonism arises in the setting of FTD, dopaminergic therapy can be attempted, although there is little evidence to suggest a benefit. Moreover, side effects such as nausea, hypotension, psychosis, and livedo reticularis are major issues that often limit the ability to escalate the dose of dopaminergic agents.

Potential disease-modifying treatments

In the past decade, knowledge has rapidly advanced regarding the pathology, genetics, and pathophysiology of the various forms of FTLT (see [Chapters 13, 14, and 15](#)). In parallel, these insights have been employed to attempt to develop strategies for interventions that would modify the underlying disease processes of FTLT.

Targets

Tau

Tau is a microtubule-associated protein localized to neuronal axons that regulates the stability of microtubules by promoting tubulin polymerization. Tau-related neuronal dysfunction in neurologic disease may occur by two non-mutually exclusive mechanisms, either gain of function or loss of function. Tau gain of function occurs when tau aggregates, which may be toxic to neurons and glia [47, 48]. Tau hyperphosphorylation is also seen in disease states, and may promote aggregation of insoluble tau species and also decrease microtubule binding, leading to loss of tau function [49]. Aggregates of hyperphosphorylated tau are found in AD and approximately half of all FTLT disorders, including Pick's disease, PSP, CBD, argyrophilic grain disease, neurofibrillary tangle dementia, and FTDP-17.

Reducing hyperphosphorylated tau aggregates and other potentially toxic tau species, altering post-translational modification of tau, such as reducing phosphorylation, or stabilization of microtubules to make up for loss of tau function may all be viable strategies for FTLT-tau therapy. The strong genetic association of tau, via mutations in microtubule-associated protein tau (*MAPT*), with FTLT provides a rationale for interventions that target tau in FTLT cases with underlying tau pathology. The strong association of the most common PSP clinical syndrome (Richardson's) with the presence of tau protein aggregates on neuropathologic examination creates a strong rationale for investigating the effects of tau-directed therapies in these patients as well.

Because many were originally intended for use in AD, tau-directed therapies are more advanced than other potential disease-modifying therapies for FTD. An underlying assumption is that tau pathology in AD is sufficiently similar to tau in FTD that the same therapies should be efficacious for both disorders. Therapeutic strategies with tau fall under four general categories: inhibition of aggregation, inhibition of phosphorylation, reduction of tau levels, and microtubule stabilization. The strongest evidence for efficacy from preclinical models of tau-mediated neurodegeneration exists for agents that reduce tau protein levels. Interestingly, a number of transgenic mouse lines that lack tau expression have been found to survive to adulthood with none to few measurable deficits.

Tau gain-of-function therapies

Methylene blue (reformulated as LMTx), an inhibitor of tau and possibly transactive response DNA-binding protein 43 (TDP-43) aggregation, completed a phase II clinical trial in AD in 2009, and is now being investigated in two phase III clinical trials for AD and bvFTD. Pathologic

tau species are frequently hyperphosphorylated. Protein kinase inhibition may prevent phosphorylation, and glycogen synthase kinase 3 (GSK3) has been an early target of therapies meant to block tau phosphorylation. Clinical trials using lithium chloride for PSP and CBD and tideglusib for PSP, both thought to be GSK3 inhibitors, were not successful because of toxicity (lithium) and lack of efficacy (tideglusib). Lithium chloride used in AD patients did not change cerebrospinal fluid (CSF) phosphorylated tau levels or GSK3 activity in serum [50]. Preliminary reports also suggest that the specific GSK3b inhibitor, tideglusib, also did not demonstrate any effects on cognitive end points in a phase IIb AD trial or a phase II trial in PSP [51, 52]. Modulating phosphatase activity to remove phosphate groups or more specific kinase inhibitors remain a possible intervention to ameliorate tau pathology and remain an active area of study. In addition, modulating other post-translational modifications of tau such as acetylation and glycation may be other promising therapeutic strategies [53]. Decreasing total tau protein levels via antisense oligonucleotide-mediated reduction of mRNA levels is actively being investigated in a number of academic laboratories and pharmaceutical companies [54].

The most advanced strategies for reducing endogenous tau levels involve immunologic approaches targeting a variety of different tau epitopes. Recent studies demonstrating that pathogenic tau species are transmitted trans-synaptically provide support for reducing tau levels in the extracellular space. Immunotherapeutic approaches to tau can be characterized as active or passive immunization. Active immunization involves introduction of foreign antigen into the subject, inducing a T-cell response and antibody generation. Active immunization raises safety concerns as previous amyloid active immunotherapy trials were associated with encephalitis. The use of smaller tau peptides may decrease the risk of inflammation while retaining the ability to generate antibodies that clear tau

pathology in the cortex [55]. Immunized transgenic mouse models with human tangle pathology have been shown to perform better on sensorimotor tests with decreased cognitive impairment [56, 57]. At least one anti-phosphorylated tau vaccine is currently in clinical development [58].

Passive immunization has the advantage of potentially fewer autoimmune side effects, and several approaches have been described in tau transgenic mice. Antibodies directed against various tau epitopes have been administered to mouse models prior to the onset of pathology, demonstrating reduction in tau tangles, pathologic tau, and improved motor tasks [59, 60]. Recently, an anti-tau monoclonal antibody that targets a pathologic form of tau that is able to seed other pathologic conformations was shown to block seeding activity and improve cognitive deficits in tau transgenic mice [61]. As this antibody is not thought to enter neurons, its mechanism of activity likely involves peripheral clearance, promotion of microglia tau uptake, or blocking trans-synaptic spread of tau species with seeding activity. In short, proof of concept has been demonstrated in animal models using both active and passive immunization approaches, with improvements in clearance of tau as well as memory and motor tasks, but human studies are still needed. It remains to be seen whether certain tau conformations are better targets for immune clearance and whether different tau conformations are associated with different tauopathies.

Tau loss-of-function therapies

Loss of tau binding to microtubules is thought to impair their function in transporting cellular constituents via a loss in MT stability [62]. Stabilization of microtubules has been proposed as a way to make up for loss of tau function. Taxanes, a class of cancer drugs derived from taxol that stabilize tubulin and a related class of compounds called epothilones, with fewer toxic side effects and better blood–brain barrier penetration have

been of interest. A recent study suggests paclitaxel may help restore synaptic function in mutant human tau neurons [63]. The leading compound in this class, epothilone D, was found in transgenic tau mouse models to improve axonal microtubule density and decreased axonal dystrophy. In addition, spatial learning deficits improved in treated mice, at a dose 1/30th to 1/10th of the dose utilized in human cancer trials [64, 65]. Epothilone D was briefly investigated in a phase I clinical trial for AD, but was abandoned for further development. Recently a peptide derived from the growth factor activity-dependent neurotrophic protein called davunetide, which may also promote microtubule stability, failed to show efficacy in a pivotal clinical trial in PSP patients (unpublished data). Despite these disappointing results, microtubule-stabilizing agents continue to be explored as potential therapies, and various similar compounds are in phase I or preclinical testing as of this writing. TPI-287, a taxane-based microtubule-stabilizing agent has entered phase I clinical trial for Alzheimer's disease [66].

TDP-43

Insoluble deposits of TDP-43 in neurons and glia are found in approximately half of FTLD cases, termed FTLD-TDP [67]. Of the FTD clinical syndromes, FTLD-TDP is strongly associated with FTD-ALS (amyotrophic lateral sclerosis) and svPPA. Two autosomal dominant forms of FTLD, FTLD due to progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9orf72*) mutations, display FTLD-TDP pathology, although TDP-43's role in the pathogenesis of these syndromes is unclear. Mutations in the TDP-43 gene (*TARBP*) itself are generally associated with an ALS phenotype; rarely these are also associated with FTD. In FTLD and ALS, aggregates of TDP-43 are hyperphosphorylated, ubiquitinated, and cleaved in the C-terminal fragments. TDP-43 is a RNA-binding protein involved in

transcription, splicing, and transport of a variety of heterogeneous RNA targets, and is essential for neural development and axon guidance. In addition, TDP-43 is able to autoregulate its expression level through a negative-feedback loop [68]. Whether TDP-43 aggregates or loss of TDP-43 function leads to neurodegeneration is under investigation. A challenge has been that numerous mouse transgenic models overexpressing mutant TDP-43 have failed to demonstrate TDP-43 aggregates despite ALS-like phenotype development [69, 70]. Yet disease progression was halted when the transgene was turned off, suggesting function may be more relevant to pathogenesis [71]. Eventual elucidation of TDP-43 function may lead to targeted therapies directed at this pathologic finding. Of note TDP-43, C9ORF72, and the fused in sarcoma protein (FUS), which is also associated with a rare but severe form of FTD (and ALS), are all involved in RNA processing, and thus general strategies to modulate RNA processing and transport may be promising therapeutic approaches to FTLD-TDP. Development of human biomarkers that can quantify abnormal TDP-43 or its associated proteins may also help FTLD-TDP patients by allowing accurate therapeutic intervention. Recently, the ratio of phosphorylated tau to total tau was shown to help identify human cases of FTLD-TDP [72]. It is hoped that tau PET imaging may also be able to differentiate FTLD-TDP cases during life; however, this has yet to be formally demonstrated [73].

Progranulin

Mutations in the progranulin gene (*GRN*) discovered in 2006 account for up to 5–10% of FTD cases with European ancestry [74]. *GRN* mutations result in haploinsufficiency of *GRN* mRNA expression, leading to a readily measurable decrease in serum and CSF levels of progranulin (PGRN) protein that may serve as a useful biomarker not only for diagnosis but also

treatment-response therapies in FTLD patients [75–77]. Endogenous molecules such as transmembrane proteins, microRNAs, and allelic variants of GRN that affect PGRN levels are suggested to affect the risk of developing FTLD-TDP [78]. In the CNS, PGRN is produced by both neurons and glia, and has neurotrophic and synaptic effects, as well as regulating the function of microglia. The physiologic role of PGRN in the CNS is an area of continued investigation, but in the periphery PGRN serves as a neurotrophic factor, and plays a role in development, wound repair, tumorigenesis, and inflammation. PGRN has a potent role in regulating systemic inflammation, where it appears to antagonize the pro-inflammatory effects of tumor necrosis factor- α (TNF- α) [79]. FTLD-TDP patients have elevated peripheral TNF- α levels, suggesting that CNS immune dysregulation may play a role in the development of FTLD [80]. Moreover, anti-PGRN antibodies are sometimes found in patients with other forms of systemic autoinflammatory disease [81].

Despite the lack of clear understanding of PGRN function, it is a promising target for FTD treatment. The measurable decreases in human blood and CSF PGRN levels provide strong evidence that decreased PGRN signaling is a cause of FTD. This implies that raising or restoring PGRN levels into the normal range might be an effective therapy for FTLD. Suberoylanilide hydroxamic acid (SAHA), a FDA-approved histone deacetylase inhibitor (HDACi), was shown to be an enhancer of PGRN expression [82]. A recent in vitro study using small molecules to decrease sortilin (SORT1) function, a neuronal receptor for PGRN endocytosis, demonstrated elevated PGRN levels in human cells [83]. Alkalizing drugs such as chloroquine, bepridil, and amiodarone that affect endosomal sorting similarly stimulate PGRN production, through a post-translational mechanism [84]. However, a recent pilot phase II study using amiodarone in five FTD patients with *GRN* mutation failed to demonstrate elevation of

peripheral GRN levels or a change in disease course when retrospectively compared with 13 FTD patients who were followed in previous years. A caveat of this study is the lack of dose-ranging studies, and final utilized dose was based on cardiologic settings [85]. A phase I clinical trial of the CNS-penetrant calcium channel blocker nimodipine is under way to determine the maximum tolerated dose and its effects on serum and CSF PGRN levels [86]. In addition, PGRN's role in inflammation may also provide novel intervention strategies as described below.

Immunogenicity

There has long been a suspicion that there is an inflammatory contribution to neurodegenerative pathogenesis. Elevations in CSF cytokines, notably TNF- α , have previously been demonstrated in FTD but without clear differentiation which pathologic subtypes were associated [87]. PGRN mutation with TDP-43 pathology has been of particular interest as it has been demonstrated that PGRN knockout mice develop inflammatory arthritis and PGRN demonstrated antagonistic effects to TNF- α signaling [79]. In addition, in one study, around 40% of rheumatoid arthritis and systemic lupus erythematosus patients had anti-PGRN antibodies that significantly lowered PGRN levels, similar to the haploinsufficiency state of PGRN mutation carriers [81]. A high prevalence of systemic autoimmune conditions and elevated levels of TNF- α in svPPA and *GRN* mutation carriers compared with Alzheimer's controls, normal controls, and general population further support the role of inflammation in FTLD-TDP. Specific autoimmune conditions found to be significantly elevated were inflammatory arthritides, such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis; cutaneous disorders; and gastrointestinal conditions [80].

The findings above suggest there may be an inflammatory role to the pathogenesis of FTD, especially in TDP-43 pathology. Decreased PGRN expression leading to increased TNF- α signaling or primary increased TNF- α signaling may contribute to FTLD-TDP. It may also be that systemic inflammation shares underlying pathogenic mechanisms with those at work in FTLD-TDP. A mounting body of evidence suggests that PGRN also plays a role in the development of AD, and cases of both FTLD-TDP and AD pathology have been described [88]. Modulation of TNF- α levels using FDA-approved anti-TNF- α agents commonly used to treat systemic autoimmune disease, such as infliximab, adalimumab, etc., may be of interest. Engineered PGRN fragments have also been developed and shown to reduce arthritis in mouse models, offering another potential approach to FTLD-PGRN therapy [79]. An exciting possibility is that an efficacious treatment for FTLD-PGRN may predict efficacy in AD and/or systemic autoimmune diseases given the overlap in pathogenic mechanisms.

C9ORF72

FTD and ALS are both neurodegenerative processes. ALS affects both upper and lower motor neurons, presenting with weakness, atrophy, and rapid progression to death; up to 22% of ALS patients meet FTD diagnostic criteria, and 48% manifest cognitive or behavioral abnormalities without meeting the full criteria. Conversely, up to 15% of FTD patients display signs of motor neuron disease or ALS [89]. Both diseases have a 10% prevalence of autosomal dominant pattern as well, suggesting some shared pathophysiology (see [Chapter 6](#)).

In 2011, a hexanucleotide repeat expansion in a 5' non-coding region of the *C9orf72* gene was found to be the cause of FTD and ALS in a strongly chromosome 9p-linked family [90–92]. Subsequent analysis revealed this

mutation to be the cause of 11.7% of familial FTD and 23% of familial FTD–ALS in one large series. Clinical phenotypes most frequently associated with this mutation are FTD, ALS, and FTD–ALS, but corticobasal syndrome, nvPPA, and svPPA with and without motor neuron disease have been described. The pathology associated with *C9orf72* mutation carriers have been overwhelmingly FTLD-TDP, specifically subtypes A and B, but also with unique p62-positive, TDP-43-negative inclusions, especially in the cerebellum and hippocampus [93].

Although the precise function of C9ORF72 remains unknown, a bioinformatics approach has recently shown that it is structurally similar to differentially expressed in normal and neoplastic cells (DENN) proteins, a class of GDP/GTP exchange factors important for Rab-GTPases, suggesting a role in vesicular trafficking [94]. Expanded repeats may result in untranslated regions causing loss of function. In addition, similar to myotonic dystrophy, expanded RNA transcripts may result in toxic nuclear inclusions that sequester other RNAs or RNA-binding proteins, a class of proteins in which both FUS and TDP-43 belong. The GGGGCC repeat RNA structure also allows for an unconventional means of translation, termed repeat-associated non-ATG (RAN) translation. Recently, antibodies generated against these RAN translation products have identified unique accumulations of poly-(glycine-proline) peptides [95]. Similar polypeptides have also been observed in myotonic dystrophy type 1 and spinal cerebellar ataxia 8. Whether this polypeptide is simply an accumulation of translated products via RAN translation or causes toxic effects remain to be seen, but may serve as a potential sensitive, specific, and early biomarker for C9ORF72 causes of FTD and ALS.

As expanded RNA transcripts may be a possible culprit of neurodegeneration, antisense oligonucleotides (ASO) may serve as a possible therapeutic strategy for FTLD due to *C9orf72* hexanucleotide

repeat expansions. ASO are synthetic nucleic acids that inactivate the mRNA of a target gene by direct binding or inducing RNase H-mediated cleavage via DNA/RNA heteroduplex. For *C9orf72* mutation carriers, this strategy is attractive as it might lower both expanded RNA transcripts and limit RAN translation. Preliminary steps for ASO treatment have been studied in ALS caused by superoxide dismutase (SOD1) and were well tolerated in animal models and a recent phase I clinical trial in human SOD1 mutation carriers [96]. ASO directed against *C9orf72* sequences have been shown to reduce *C9orf72* RNA expansion-dependent pathology in cultured neurons derived from human C9ORF72-induced pluripotent stem cells (iPS) [97]. Furthermore, injection of ASO directed against *C9orf72* sequences into mice did not demonstrate behavioral or neuropathologic abnormalities, suggesting that broad reduction of *C9orf72* translation is likely to be safe [98].

The discovery of C9ORF72 may reveal important mechanistic information about the molecular pathophysiology of FTD and ALS and may provide novel treatment strategies. If loss of function is implicated, strategies to increase levels of C9ORF72 or augment C9ORF72 function may be needed. If expanded RNA transcripts are responsible, ongoing clinical trials for non-coding repeat expansion disease such as myotonic dystrophy type 1 (DM1) and fragile X-associated tremor/ataxia syndrome (FXTAS) may provide starting points for decreasing RNA transcription or altering RNA structure and aggregation. ASOs may be a unique, targeted therapy for patients carrying the *C9orf72* expansion. The discovery of poly-(glycine-proline) peptides may provide a useful early, sensitive and specific biomarker for C9ORF72 causes of FTD, both diagnostically and as a pharmacodynamic tool, allowing for accurate targeted intervention.

Models

Drug development for rare diseases such as FTD may be challenging since the ability to conduct multiple, large, concomitant human clinical trials is limited. Thus, preclinical studies in FTD treatment will likely share a greater weight in risk and understanding of FTD-related drug development. Preclinical models must be scrutinized against three criteria: (1) relevance to the human disease state, (2) pharmacologic applicability, and (3) internal validity and consistency. Many transgenic models at best recapitulate rare genetic causes of sporadic disease and may present novel mechanisms different from humans. For example, in the field of diabetes, human studies suggest that loss-of-function mutations of *SLC30A8*, a gene that codes for an insulin-related zinc transporter protein, may provide protection against type 2 diabetes. However, previous animal model studies have suggested increased type 2 diabetes risk in mouse *Slc30a8* knockouts [99]. Preclinical models need to provide pharmacokinetic and pharmacodynamic measures relevant to human use; thus models or species that fail to yield these data – for example, models that require intrathecal administration – will be undesirable. Finally, there is some concern of stability of animal models owing to genetic drift, age, or other environmental factors. Thus models should show generational consistency with predictable phenotype–disease pathophysiology relationships [54]. The following section will provide a brief overview of available cell and animal models for FTD treatment development (see [Chapter 15](#) for more details).

Pluripotent stem cells

Induced pluripotent stem (iPS) cells are pluripotent stem cells generated from adult cells. First pioneered in 2006 and later refined, the introduction of pluripotency-associated genes into human fibroblasts reprogrammed

these cells to exhibit embryonic stem cell traits [100]. These cells can then be differentiated into a variety of cell types, such as neuronal precursors or neurons. The use of iPS cells is attractive for several reasons. It limits the significant differences in physiology and toxicology between animals and humans, and it avoids the technical and ethical challenges involved in using human embryonic stem cells. Recently, iPS cell lines for *C9orf72* mutation, PGRN mutation, and tau have been developed [101–103]. These cell lines will likely provide a novel platform closely related to human pathology for drug development. Patient-derived iPS cells are rapidly becoming a powerful tool for drug discovery, but several caveats should still be kept in mind. The characterization of cells to ensure the correct cell line is produced is crucial. There is a considerable time investment compared with other models, for example human astrocytes take up to 12–24 weeks to develop, and may resemble more immature cells as compared to mature cell types. In iPS cell experiments there are typically various other cells in the dish that may affect intervention outcomes. Finally, one must carefully monitor the variations possible in developing iPS cells, such as line-specific variations with regard to methods used to reprogram the cells as well as the donors of the cells themselves.

Mouse

Mouse models are attractive as there has already been considerable experience invested in mouse model development for other neurodegenerative disease, such as AD, which shares tau pathology with FTD. In addition, mouse models allow behavioral outcomes to be measured, providing close relationships to FTD phenotypes. Social dysfunction, repetitive behavior, and memory tasks that can be measured

should provide useful advantages to using mouse models as it allows a functional measurement of neurodegeneration.

Numerous lines of transgenic mice expressing human tau mutations have been created, with diverse transgenic protein expression and hence diverse neuropathologic and behavioral phenotype [104]. Although previous experiences have shown tau pathology to be closely related to cognitive decline, it is important to note that a mouse model previously demonstrated a dissociation of cognitive deficits from neurofibrillary tangle pathology [105]. This finding illustrates the importance of validity and relevance. The ability to identify the correct species of tau responsible for toxicity and phenotypic changes and whether it translates to human pathology will be crucial in efficient drug development against tau.

There is less substantial experience with TDP-43 mouse models, and as mentioned above, the mechanism by which TDP-43 is associated with FTD is less clear. The relatively weak genetic association between TDP-43 gene (*TARBP*) mutations and FTD is also a barrier to our understanding. Transgenic mice with calcium/calmodulin-dependent kinase type 2-driven full-length mouse TDP demonstrated behavioral impairment [106]. In addition, as mentioned above, ALS models with TDP-43 pathology have been developed, but the exact relation between TDP-43 function, aggregation, and pathophysiology remain unclear. *GRN* mutations are also relevant to TDP-43 proteinopathy. Although PGRN function remains to be elucidated, its known mutation and haploinsufficiency lends itself to exciting models with measurable levels that may serve as biomarkers. Heterozygous PGRN knockout mice have been developed that demonstrate age-dependent emotional and social deficits potentially relevant to FTD, with one model demonstrating abnormalities without neuroinflammation [107, 108]. A separate mouse model utilizing human tau and knockout CX3CR1, a receptor thought to be crucial in neuroinflammation, demonstrated

aggregated hyperphosphorylated tau and behavior changes [109]. The complex interplay between TDP-43, PGRN, inflammation, and tau demonstrated by the mouse models suggest that there may be multiple causes leading to the heterogeneous FTD phenotype, and multiple targeted therapies will be needed.

Other

Other animal models developed for study of FTD include the nematode *Caenorhabditis elegans*, fruitfly *Drosophila melanogaster*, and zebra fish *Danio rerio*. *Caenorhabditis elegans* present with the opportunity to study genetic pathogenesis in a well-described nervous system with proven techniques to monitor behavior, learning, and memory. *Drosophila melanogaster* models are relatively inexpensive and have rapid life cycles, facilitating identification of genetic enhancers and suppressors. The zebra fish has historically been used as a model for vertebrate development. The zebra fish shares phylogenetic conservation with other vertebrates, and its larvae can be readily exposed to chemicals, which may serve as an effective means for drug screening. Additional details for the above models were reviewed previously [54].

Future directions

Rapid development of successful FTD therapies will require close collaboration between academic laboratories, clinical research centers, the pharmaceutical industry, and the FDA. The cooperation of the pharmaceutical industry is especially critical with its large therapeutic compound libraries, clinical trials expertise, funding, and established infrastructure. The recent davunetide trial for PSP, although unsuccessful,

has proven that international, multicenter clinical trials for rare neurodegenerative diseases are feasible. The recently launched Dominantly Inherited Alzheimer's Network (DIAN) treatment unit, Alzheimer's Prevention Initiative (API), and Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) studies are all aimed at presymptomatic patients. DIAN is a network of academic centers originally formed to research autosomal dominant familial AD. It is now conducting an international, multicenter, placebo-controlled clinical trial utilizing a multi-drug adaptive design in patients at risk for genetic AD. Along similar lines, the API was initiated by Banner Alzheimer's Institute, along with the National Institutes of Health, Genentech, and University of Antioquia's Grupo de Neurociencias in Medellin, Colombia, to study a large extended family in Colombia and patients in the USA with a rare form of autosomal dominant AD. Finally, A4 is a large, landmark public–private partnership initiated by academic centers, coordinated by the Alzheimer's Disease Cooperative Study, funded by the National Institute on Aging, philanthropic organizations, and Eli Lilly and Company, aimed at studying anti-amyloid therapy in asymptomatic individuals who test positive for fibrillar amyloid via positron emission topography imaging and may be at risk for AD. These large trials have shown that academic-led clinical trials with industry assistance can be developed on a worldwide scale. Continued successful collaboration between academic and industry partners will rely on partnerships in design and eventual transparency of data sharing, as even unsuccessful trials can provide valuable lessons in understanding disease physiology and future clinical trial planning.

Industry cooperation

FTD has a great unmet medical need with no FDA-approved therapies and may have several attractive characteristics for industry participation. The lack of effective therapies has translated into highly motivated patients and caregivers in clinical trial participation, which may reduce recruitment time. As few drugs are beneficial symptomatically, there are few exclusion criteria when it comes to concomitant medications. A large fraction of FTD pathology involves tau, which provides a synergistic motivation as many pharmaceutical companies are also involved in Alzheimer's treatment research. In addition, it is less likely than AD to involve pathology which is mixed with other proteinopathies or vascular disease [110]. FTD patients are younger and less likely to develop mixed pathologies that may affect treatment efficacy. PSP may be an especially attractive target as it has a consistent, measurable phenotype and is frequently associated with tauopathy. The rarity of FTD and its related disorders also allows clinical trials to apply for orphan drug status with the FDA, leading to accelerated approval. Finally, a first-to-market FTD therapy will be strongly positioned and may lead to rapid development of indications for other FTD-related disorders.

Clinical trial considerations

Aside from the gold standard of randomized, double-blind, controlled trials, treatment development requires sensitive clinical rating scales validated in FTD phenotypes. As previously reviewed by Boxer *et al.*, a number of cognitive, behavior, and motor scales have been studied and validated in longitudinal studies of FTD phenotype [54]. An important phenomenon to note is that NPI scores in FTD patients may improve over time without intervention, owing to the increased levels of apathy and withdrawal [111]. However, this does not preclude their meaningful use in FTLD clinical

trials [46]. Functional rating scales may be more sensitive than psychiatric measurements in FTD patients when measuring long-term progression. Rating scales should be sensitive in reflecting change over time, and facilitate translation and transport across sites as future FTD trials will likely be multinational and involve patients from various cultural backgrounds.

Differentiating between the various pathologic subtypes of FTD will be important for proper patient selection in targeted pharmacologic intervention, and biomarkers provide a potential solution. Biomarkers can also provide an attractive, physiology-based measurement that may provide additional support for the efficacy of pharmacologic interventions. Most FTD biomarkers to date have focused on differentiating FTD from AD, and these include CSF amyloid- β and tau; and amyloid-sensitive PET using Pittsburgh compound B and other ligands. Recent studies have suggested that neurofilament light chain, a cytoskeleton constituent of intermediate filaments thought to reflect neuronal damage, may also be useful for differentiating FTD subtypes [112, 113]. CSF neurofilament light chain may be sensitive to disease progression and the level of serum and CSF PGRN may be promising pharmacodynamic biomarkers in clinical trials aimed at elevating PGRN levels. Imaging techniques focused on volumetric MRI may also be useful for tracking disease progression, as previous studies have shown FTD patients with *MAPT* or *GRN* mutations with distinct rates of atrophy [114].

Additional longitudinal clinical, imaging, and biomarker data for various FTD subpopulations will be helpful for planning clinical trials. The recently completed davunetide trial contains longitudinal MRI brain data for over 200 PSP patients and will likely provide significant information as well. Tau imaging using PET scans is an exciting new development, with a recently identified ligand ^{11}C -PBB3 showing sensitive detection of tau

inclusions in mouse models and AD patients [73]. Tau imaging may in the near future allow accurate identification of patients suitable for tau-targeted therapy, and also allow tracking of therapy efficacy through tau clearance.

Secondary prevention in familial FTD cases is an important concept that deserves mention. These are patients known to have a high chance of developing FTD symptoms and FTD has a much higher percentage of familial cases than AD, which increases the importance of conducting such trials. It is now known that familial AD pathology is present years before symptom onset [115]. The same may be true for familial FTD cases. In addition, familial FTD often provides insight to the responsible pathologic protein by virtue of gene mutation, allowing correct selection of treatment agent. There is precedence for treatment in the asymptomatic phase of such patients as described in the DIAN and API trials above. Such groundbreaking treatment trials have provided precedence on how to manage ethical, genetic, and consent concerns as well as strategies for international, cross-cultural cooperation. Currently, multicenter coordinated efforts to study familial FTD cases have begun in Europe under the Genetic Frontotemporal dementia Initiative (GENFI), and similar efforts in the USA are underway. Challenges unique to familial FTD treatment trials include the relatively low number of available cases worldwide despite occupying a higher percentage of total FTD cases, and the variable age of onset and disease progression will cause significant difficulties in outcomes measurement.

Finally, there are substantial regulatory considerations when performing clinical trials in FTD. Currently the FDA has limited experience in FTD clinical trials and there is limited well-established precedent. As FTD is a rare, serious, and life-threatening illness, treatments may qualify for accelerated approval, or other conditional mechanisms relying on a surrogate outcome such as a biomarker under subpart H of FDA regulations.

Ultimately, a clear and meaningful effect on survival, morbidity, or a well-established measurement of clinical disease will likely be needed for approval of an FTLT-Indicated treatment.

Conclusions

FTD and related disorders are a spectrum of uniformly fatal neurodegenerative diseases with a heterogeneous pathophysiology that has yet to be elucidated completely. Currently there are no FDA-approved treatments and presently used interventions provide only minimal symptomatic relief, often based on minimal clinical evidence. Recent advancements in understanding the molecular and genetic basis of FTD have reached sufficient maturity for plausible intervention targets to be identified. Potential disease-modifying therapies with sound scientific rationale are being developed based on this knowledge. Advanced animal and cell models will help accelerate this process and identify appropriate compounds. Various advantages in developing therapy for FTD should attract industry participation, and the creation of academic–industry participation under well-formulated infrastructures will greatly expedite the process from discovery to approval. With such a road map in place, it may well be a promising decade for therapy for FTD and its related disorders.

References

1. Kaye ED, Petrovic-Poljak A, Verhoeff NP, Freedman M. Frontotemporal dementia and pharmacologic interventions. *J Neuropsychiatry Clin Neurosci* 2010;22(1):19–29.
2. Angoa-Perez M, Kane MJ, Briggs DI, Sykes CE, Shah MM, Francescutti

DM, *et al.* Genetic depletion of brain 5HT reveals a common molecular pathway mediating compulsivity and impulsivity. *J Neurochem* 2012;**121**:974–84.

3. Procter AW, Qurne M, Francis PT. Neurochemical features of frontotemporal dementia. *Dement Geriatr Cogn Disord* 1999;**10** Suppl 1:80–4.

4. Franceschi M, Anchisi D, Pelati O, Zuffi M, Matarrese M, Moresco RM, *et al.* Glucose metabolism and serotonin receptors in the frontotemporal lobe degeneration. *Ann Neurol* 2005;**57**:216–25.

5. Yang Y, Schmitt HP. Frontotemporal dementia: evidence for impairment of ascending serotonergic but not noradrenergic innervations. Immunocytochemical and quantitative study using a graph method. *Acta Neuropathol* 2001;**101**:256–70.

6. Hermann N, Black SE, Chow T, Cappell J, Tang-Wai DF, Lanctôt KL. Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. *Am J Geriatr Psychiatry* 2012;**20**:789–97.

7. Swartz JR, Miller BL, Lesser IM, Darby AL. Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors. *J Clin Psychiatry* 1997;**58**:212–16.

8. Chow TW, Mendez MF. Goals in symptomatic pharmacologic management of frontotemporal lobar degeneration. *Am J Alzheimers Dis Other Dement* 2002;**17**:276–72.

9. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Frontotemporal dementia: paroxetine as a possible treatment of behavioral symptoms. A randomized, controlled, open 14-month study. *Eur Neurol* 2003;**49**:13–19.

10. Mendez MF, Shapira JS, Miller BL. Stereotypical movements and frontotemporal dementia. *Mov Disord* 2005;**20**:742–5.

11. Anneser JM, Jox RJ, Borasio GD. Inappropriate sexual behavior in a case of

ALS and FTD: successful treatment with sertraline. *Amyotroph Lateral Scler* 2007;**8**:189–90.

12. Prodan CI, Monnon M, Ross ED. Behavioral abnormalities associated with rapid deterioration of language functions in semantic dementia respond to sertraline. *J Neurol Neurosurg Psychiatry* 2009;**80**:1416–17.

13. Ikeda M, Shigenobu K, Fukuhara R, Hokoishi K, Maki N, Nebu A, *et al.* Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. *Dement Geriatr Cogn Disord* 2004;**17**:117–21.

14. Furlan JC, Henri-Bhargava A, Freedman M. Clomipramine in the treatment of compulsive behavior in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord* 2014;**28**:95–8.

15. Deakin JB, Rahman S, Nestor PJ, Hodges JR, Sahakian BJ. Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial. *Psychopharmacology(Berl)* 2004;**172**:400–8.

16. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomized, controlled trial with trazodone. *Dement Geriatr Cogn Disord* 2004;**17**:355–9.

17. Huey ED, Putnam KT, Grafman J. A systematic review of neurotransmitter deficits and treatments. *Neurology* 2006;**66**:17–22.

18. Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G, Bava A. Rivastigmine in frontotemporal dementia: an open-label study. *Drugs Aging* 2004;**21**:93–107.

19. Kertesz A, Morlog D, Light M, Blair M, Davidson W, Jesso S, *et al.* Galantamine in frontotemporal dementia and primary progressive aphasia. *Dement Geriatr Cogn Disord* 2008;**25**:178–85.

-
- 20.** Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. *Am J Geriatr Psychiatry* 2007;**15**:84–7.
-
- 21.** Kimura T, Takamatsu J. Pilot study of pharmacological treatment for frontotemporal dementia: risk of donepezil treatment for behavioral and psychological symptoms. *Geriatr Gerontol Int* 2013;**13**:506–7.
-
- 22.** Rinne JO, Laine M, Kaasinen V, Norvasuo-Heilä MK, Någren K, Helenius H. Striatal dopamine transporter and extrapyramidal symptoms in frontotemporal dementia. *Neurology* 2002;**58**:1489–93.
-
- 23.** Sperfeld AD, Collatz MB, Baier H, Palmbach M, Storch A, Schwarz J, *et al.* FTDP-17: an early-onset phenotype with parkinsonism and epileptic seizures caused by a novel mutation. *Ann Neurol* 1999;**46**:708–15.
-
- 24.** Kanazawa I, Kwak S, Sasaki H, Muramoto O, Mizutani T, Hori A, *et al.* Studies on neurotransmitter markers of the basal ganglia in Pick's disease, with special reference to dopamine reduction. *J Neurol Sci* 1988;**83**:63–74.
-
- 25.** Curtis RC, Resch DS. Case of Pick's central lobar atrophy with apparent stabilization of cognitive decline after treatment with risperidone. *J Clin Psychopharmacol* 2000;**20**:384–5.
-
- 26.** Fellgiebel A, Müller MJ, Hiemke C, Bartenstein P, Schreckenberger M. Clinical improvement in a case of frontotemporal dementia under aripiprazole treatment corresponds to partial recovery of disturbed frontal glucose metabolism. *World J Biol Psychiatry* 2007;**8**:123–6.
-
- 27.** Reeves RR, Perry CL. Aripiprazole for sexually inappropriate vocalizations in frontotemporal dementia. *J Clin Psychopharmacol* 2013;**33**:145–6.
-
- 28.** Moretti R, Torre P, Antonello RM, Cazzato G, Griggio S, Bava A. Olanzapine as a treatment of neuropsychiatric disorders of Alzheimer's disease

and other dementias: a 24-month follow-up of 68 patients. *Am J Alzheimers Dis Other Dement* 2003;**18**:205–14.

29. Huey ED, Garcia C, Wassermann EM, Tierney MC, Grafman J. Stimulant treatment of frontotemporal dementia in 8 patients. *J Clin Psychiatry* 2008;**69**:1981–2.

30. Pijnenburg YA, Sampson EL, Harvey RJ, Fox NC, Rossor MN. Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. *Int J Geriatr Psychiatry* 2003;**18**:67–72.

31. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Effects of selegiline on fronto-temporal dementia: a neuropsychological evaluation. *Int J Geriatr Psychiatry* 2002;**17**:391–2.

32. Rahman S, Robbins TW, Hodges JR, Mehta MA, Nestor PJ, Clark L, *et al.* Methylphenidate (‘Ritalin’) can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. *Neuropsychopharmacology* 2006;**31**:651–8.

33. Reed DA, Johnson NA, Thompson C, Weintraub S, Mesulam MM. A clinical trial of bromocriptine for treatment of primary progressive aphasia. *Ann Neurol* 2004;**56**:750.

34. Poetter CE, Stewart JT. Treatment of indiscriminate, inappropriate sexual behavior in frontotemporal dementia with carbamazepine. *J Clin Psychopharmacol* 2012;**31**:137–8.

35. Cruz M, Marinho V, Fontenelle LF, Engelhardt E, Laks J. Topiramate may modulate alcohol abuse but not other compulsive behaviors in frontotemporal dementia: case report. *Cogn Behav Neurol* 2008;**21**:104–6.

36. Nestor PJ. Reversal of abnormal eating and drinking behavior in a frontotemporal lobar degeneration patient using low-dose topiramate. *J Neurol Neurosurg Psychiatry* 2012;**83**:349–50.

-
- 37.** Singam C, Walterfang M, Mocellin R, Evans A, Velakoulis D. Topiramate for abnormal eating behavior in frontotemporal dementia. *Behav Neurol* 2013;**27**:285–6.
-
- 38.** Shinagawa S, Tsuno N, Nakayama K. Managing abnormal eating behaviors in frontotemporal lobar degeneration in patients with topiramate. *Psychogeriatrics* 2013;**13**:58–61.
-
- 39.** Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* 2003;**348**:1333–41.
-
- 40.** Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Geergel I, *et al.* Memantine treatment in patients with moderate to severe Alzheimer Disease already receiving donepezil. *JAMA* 2004;**291**:317–24.
-
- 41.** Diehl-Schmid J, Förstl H, Pernecky R, Pohl C, Kurz A. A 6-month, open-label study of memantine in patients with frontotemporal dementia. *Int J Geriatr Psychiatry* 2008;**23**:754–9.
-
- 42.** Cummings JL, Schneider E, Tariot PN, Graham SM; Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil. *Neurology* 2006;**67**:57–63.
-
- 43.** Swanberg MM. Memantine for behavioral disturbances in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord* 2007;**21**:164–6.
-
- 44.** Boxer AL, Lipton AM, Womack K, Merrilees J, Neuhaus J, Pavlic D, *et al.* An open-label study of memantine treatment in 3 subtypes of frontotemporal lobar degeneration. *Alzheimer Dis Assoc Disord* 2009;**23**:211–17.
-
- 45.** Vercelletto M, Boutoleau-Bretonnière C, Volteau C, Puel M, Auriacombe S, Sarazin M, *et al.* Memantine in behavioral variant frontotemporal dementia: negative results. *J Alzheimer Dis* 2011;**23**:749–59.
-

46. Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, *et al.* Memantine in patients with frontotemporal lobar degeneration: a multicenter, randomized, double-blind, placebo-controlled trial. *Lancet Neurol* 2013;**12**:149–56.

47. Khlistunova I, Biernat J, Wang Y, Pickhardt M, von Bergen M, Gazova Z, *et al.* Inducible expression of tau repeat domain in cell models of tauopathy: aggregation is toxic to cells but can be reversed by inhibitor drugs. *J Biol Chem* 2006;**281**:1205–14.

48. Van der Jeugd A, Hochgräfe K, Ahmed T, Decker JM, Sydow A, Hofmann A, *et al.* Cognitive defects are reversible in inducible mice expressing pro-aggregant full-length human tau. *Acta Neuropathol* 2012;**123**:787–805.

49. Bramblett GT, Goedert M, Jakes R, Merrick SE, Trojanowski JQ, Lee VM. Abnormal tau phosphorylation at Ser396 in Alzheimer's disease recapitulates development and contributes to reduced microtubule binding. *Neuron* 1993;**10**:1089–99.

50. Hampel H, Ewers M, Bürger K, Annas P, Mörtberg A, Bogstedt A, *et al.* Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicenter 10-week study. *J Clin Psychiatry* 2009;**70**:922–31.

51. Tolosa E, Litvan I, Höglinger GU, Burn D, Lees A, Andrés MV, *et al.* A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. *Mov Disord* 2014;**29**:470–8. Feb 14. doi: 10.1002/mds.25824. [Epub ahead of print]

52. Zeltia [internet] [place unknown][publisher unknown] [Oct 2012] Available from <http://www.zeltia.es/media/docs/esflsziq.pdf?ie=UTF-8&oe=UTF8&q=prettyphoto&iframe=true&width=100%&height=100%>

53. Min SW, Cho SH, Zhou Y, Schroeder S, Haroutunian V, Seeley WW, *et al.* Acetylation of tau inhibits its degradation and contributes to tauopathy. *Neuron*

2010;**67**:853–66.

54. Boxer AL, Gold M, Huey E, Gao FB, Burton EA, Chow T, *et al.* Frontotemporal degeneration, the next therapeutic frontier: molecules and animal models for frontotemporal degeneration drug development. *Alzheimers Dement* 2013;**9**:176–88.

55. Boimel M, Grigoriadis N, Lourbopoulos A, Haber E, Abramsky O, Rosenmann H. Efficacy and safety of immunization with phosphorylated tau against neurofibrillary tangles in mice. *Exp Neurol* 2010;**224**:472–85.

56. Asuni AA, Boutajangout A, Quartermain D, Sigurdsson EM. Immunotherapy targeting pathological tau conformers in a tangle mouse model reduces brain pathology with associated functional improvements. *J Neurosci* 2007;**27**:9115–29.

57. Boutajangout A, Quartermain D, Sigurdsson EM. Immunotherapy targeting pathological tau prevents cognitive decline in a new tangle mouse model. *J Neurosci* 2010;**30**:16559–66.

58. Fierce Biotech [internet][place unknown][publisher unknown][Jan 2014] Available from <http://www.fiercevaccines.com/story/ac-immune-begins-first-trial-tau-targeting-alzheimers-vaccine/2014-01-13>

59. Boutajangout A, Ingadottir J, Davies P, Sigurdsson EM. Passive immunization targeting pathological phospho-tau protein in a mouse model reduces functional decline and clears tau aggregates from the brain. *J Neurochem* 2011;**118**:658–67.

60. Chai X, Wu S, Murray TK, Kinley R, Cella CV, Sims H, *et al.* Passive immunization with anti-tau antibodies in two transgenic models: reduction of tau pathology and delay of disease progression. *J Biol Chem* 2011;**286**:34457–67.

61. Yanamandra K, Kfoury N, Jiang H, Mahan TE, Ma S, Maloney SE, *et al.* Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease

pathology and improve cognition in vivo. *Neuron* 2013;**80**:402–14.

62. Higuchi M, Lee VM, Trojanowski JQ. Tau and axonopathy in neurodegenerative disorders. *Neuromolecular Med* 2002;**2**:131–50.

63. Erez H, Shemesh OA, Spira ME. Rescue of tau-induced synaptic transmission pathology by paclitaxel. *Front Cell Neurosci* 2014;**8**:34. doi: 10.3389/fncel.2014.00034

64. Brunden KR, Ballatore C, Lee VM, Smith AB 3rd, Trojanowski JQ. Brain-penetrant microtubule-stabilizing compounds as potential therapeutic agents for tauopathies. *Biochem Soc Trans* 2012;**40**:661–6.

65. Barten DM, Fanara P, Andorfer C, Hoque N, Wong PY, Husted KH, *et al.* Hyperdynamic microtubules, cognitive deficits, and pathology are improved in tau transgenic mice with low doses of the microtubule-stabilizing agent BMS-241027. *J Neurosci* 2012;**32**:7137–45.

66. ClinicalTrials.gov [internet][place unknown][NIH][Oct 2013]
<http://clinicaltrials.gov/ct2/show/NCT01966666?term=tpi+287&rank>

67. MacKenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, *et al.* Nomenclature for neuropathological subtypes of frontotemporal lobar degeneration: consensus recommendations. *Acta Neuropathol* 2009;**117**:15–18.

68. Sephton CF, Cenik B, Cenik BK, Herz J, Yu G. TDP-43 in central nervous system development and function: clues to TDP-43 associated neurodegeneration. *Biol Chem* 2012;**393**:589–94.

69. Arnold ES, Ling SC, Huelga SC, Lagier-Tourenne C, Polymenidou M, Ditsworth D, *et al.* ALS-linked TDP-43 mutations produce aberrant RNA splicing and adult-onset motor neuron disease without aggregation or loss of nuclear TDP-43. *Proc Natl Acad Sci USA* 2013;**110**:E736–45.

70. Janssens J, Wils H, Kleinberger G, Joris G, Cuijt I, Ceuterick-de Groote C,

et al. Overexpression of ALS-associated p.M337V human TDP-43 in mice worsens disease features compared to wild-type human TDP-43 mice. *Mol Neurobiol* 2013;**48**:22–35.

71. Huang C, Tong J, Bi F, Zhou H, Xia XG. Mutant TDP-43 in motor neurons promotes the onset and progression of ALS in rats. *J. Clin Invest* 2012;**122**:107–18.

72. Hu WT, Watts K, Grossman M, Glass J, Lah JJ, Hales C, *et al.* Reduced CSF p-tau181 to tau ratio is a biomarker for FTLD-TDP. *Neurology* 2013;**81**:1945–52.

73. Maruyama M, Shimada H, Suhara T, Shinotoh H, Ji B, Maeda J, *et al.* Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron* 2013;**79**(6):1094–108.

74. van Swieten JC, Heutink P. Mutations in progranulin (*GRN*) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia. *Lancet Neurol* 2008;**7**:965–74.

75. Finch N, Baker M, Crook R, Swanson K, Kuntz K, Surtees R, *et al.* Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members. *Brain* 2009;**132**:583–91.

76. Ghidoni R, Benussi L, Ghittoni M, Franzoni M, Binetti G. Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration. *Neurology* 2008;**71**:1235–39.

77. Sleegers K, Brouwers N, Van Damme P, Engelborghs S, Gijselinck I, van der Zee J, *et al.* Serum biomarker for progranulin-associated frontotemporal lobar degeneration. *Ann Neurol* 2009;**65**:603–9.

78. Rademakers R, Eriksen JL, Baker M, Robinson T, Ahmed Z, Lincoln SJ, *et al.* Common variation in the miR-659 binding-site of *GRN* is a major risk factor for TDP43-positive frontotemporal dementia. *Hum Mol Genet* 2008;**17**:3631–

79. Tang W, Lu Y, Tian QY, Zhang Y, Guo FJ, Liu GY, *et al.* The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. *Science* 2011;**332**:478–84.

80. Miller ZA, Rankin KP, Graff-Radford NR, Takada LT, Sturm VE, Cleveland CM, *et al.* TDP-43 frontotemporal lobar degeneration and autoimmune disease. *J Neurol Neurosurg Psychiatry* 2013;**84**:956–62.

81. Thurner L, Preuss KD, Fadle N, Regitz E, Klemm P, Zaks M, *et al.* Progranulin antibodies in autoimmune disease. *J Autoimmun* 2013;**42**:29–38.

82. Cenik B, Sephton CF, Dewey CM, Xian X, Wei S, Yu K, *et al.* Suberoylanilide hydroxamic acid (vorinostat) up-regulates progranulin transcription: rational therapeutic approach to frontotemporal dementia. *J Biol Chem* 2011;**286**:16101–8.

83. Lee WC, Almeida S, Prudencio M, Caulfield TR, Zhang YJ, Bauer PO, *et al.* Targeted manipulation of the sortilin-progranulin axis rescues progranulin haploinsufficiency. *Hum Mol Genet* 2014;**23**(6):1467–78. doi: 10.1093/hmg/ddt534. [Epub 2013]

84. Capell A, Liebscher S, Fellerer K, Brouwers N, Willem M, Lammich S, *et al.* Rescue of progranulin deficiency associated with frontotemporal lobar degeneration by alkalizing reagents and inhibition of vacuolar ATPase. *J Neurosci* 2011;**31**:1885–94.

85. Alberici A, Archetti S, Pilotto A, Premi E, Cosseddu M, Bianchetti A, *et al.* Results from a pilot study on amiodarone administration in monogenic frontotemporal dementia with granulin mutation. *Neurol Sci* 2014;**35**(8):1215–19.

86. ClinicalTrials.gov [internet][place unknown][NIH][Mar 2013]
[http://clinicaltrials.gov/ct2/show/NCT01835665?](http://clinicaltrials.gov/ct2/show/NCT01835665?term=progranulin+nimodipine&rank=1)
[term=progranulin+nimodipine&rank=1](http://clinicaltrials.gov/ct2/show/NCT01835665?term=progranulin+nimodipine&rank=1)

-
- 87.** Sjögren M, Folkesson S, Blennow K, Tarkowski E. Increased intrathecal inflammatory activity in frontotemporal dementia: pathophysiological implications. *J Neurol Neurosurg Psychiatry* 2004;**75**:1574–6.
-
- 88.** Perry DC, Lehmann M, Yokoyama JS, Karydas A, Lee JJ, Coppola G, *et al.* Progranulin mutations as risk factors for Alzheimer disease. *JAMA Neurol* 2013;**70**:77477–8.
-
- 89.** Sha SJ, Boxer A. Treatment implications of *C9ORF72*. *Alzheimers Res Ther* 2012;**4**:46.
-
- 90.** Boxer AL, Mackenzie IR, Boeve BF, Baker M, Seeley WW, Crook R, *et al.* Clinical, neuroimaging and neuropathological features of a new chromosome 9p-linked FTD-ALS family. *J Neurol Neurosurg Psychiatry* 2011;**82**:196–203.
-
- 91.** DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, *et al.* Expanded GGGGCC hexanucleotide repeat in noncoding region of *C9ORF72* causes chromosome 9p-linked FTD and ALS. *Neuron* 2011;**72**:245–56.
-
- 92.** Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, *et al.* A hexanucleotide repeat expansion in *C9ORF72* is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 2011;**72**:257–68.
-
- 93.** Al-Sarraj S, King A, Troakes C, Smith B, Maekawa S, Bodi I, *et al.* p62 positive, TDP-43 negative, neuronal cytoplasmic and intranuclear inclusions in the cerebellum and hippocampus define the pathology of *C9orf72*-linked FTLD and MND/ALS. *Acta Neuropathol* 2011;**122**:691–702.
-
- 94.** Levine TP, Daniels RD, Gatta AT, Wong LH, Hayes MJ. The product of *C9orf72*, a gene strongly implicated in neurodegeneration, is structurally related to DENN Rab-GEFs. *Bioinformatics* 2013;**29**:499–503.
-
- 95.** Ashe PE, Bieniek KF, Gendron TF, Caulfield T, Lin WL, DeJesus-

Hernandez M, *et al.* Unconventional translation of *C9ORF72* GGGGCC expansion generates insoluble polypeptides specific to c9FTD/ALS. *Neuron* 2013;**77**(4):639–46.

96. Miller T, Pestronk A, David W, Rothstein J, Simpson E, Appel SH, *et al.* An antisense oligonucleotide against *SOD1* delivered intrathecally for patients with *SOD1* familial amyotrophic lateral sclerosis: a phase 1, randomized, first-in-man study. *Lancet Neurol* 2013;**12**:435–42.

97. Donnelly CJ, Zhang PW, Pham JT, Heusler AR, Mistry NA, Vidensky S, *et al.* RNA toxicity from the ALS/FTD *C9ORF72* expansion is mitigated by antisense intervention. *Neuron* 2013;**80**:415–28.

98. Lagier-Tourenne C, Baughn M, Rigo F, Sun S, Liu P, Li HR, *et al.* Targeted degradation of sense and antisense *C9orf72* RNA foci as therapy for ALS and frontotemporal degeneration. *Proc Natl Acad Sci USA* 2013;**110**:E4530–9.

99. Flannick J, Thorleifsson G, Beer NL, Jacobs SB, Grarup N, Burt NP, *et al.* Loss-of-function mutations in *SLC30A8* protect against type 2 diabetes. *Nat Genet* 2014;**46**(4):357–63. doi: 10.1038/ng.2915.

100. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007;**131**:861–72.

101. Almeida S, Gascon E, Tran H, Chou HJ, Gendron TF, Degroot S, *et al.* Modeling key pathological features of frontotemporal dementia with *C9ORF72* repeat expansion in iPSC derived-human neurons. *Acta Neuropathol* 2013;**126**:385–99.

102. Almeida S, Zhang Z, Coppola G, Mao W, Futai K, Karydas A, *et al.* Induced pluripotent stem cell models of progranulin-deficient frontotemporal dementia uncover specific reversible neuronal defects. *Cell Rep* 2012;**2**:789–98.

103. Fong H, Wang C, Knoferle J, Walker D, Balestra ME, Tong LM, *et al.*

Genetic correction of tauopathy phenotypes in neurons derived from human induced pluripotent stem cells. *Stem Cell Reports* 2013;**1**:226–34.

104. Alzforum [internet][publisher unknown][date unknown] Available from <http://www.alzforum.org/research-models>

105. Santacruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, *et al.* Tau suppression in a neurodegenerative mouse model improves memory function. *Science* 2005;**309**:476–81.

106. Tsai KJ, Yang CH, Fang YH, Cho KH, Chien WL, Wang WT, *et al.* Elevated expression of TDP-43 in the forebrain of mice is sufficient to cause neurological and pathological phenotypes mimicking FTL-D-U. *J Exp Med* 2010;**207**:1661–73.

107. Yin F, Dumont M, Banerjee R, Ma Y, Li H, Lin MT, *et al.* Behavioral deficits and progressive neuropathology in progranulin-deficient mice: a mouse model of frontotemporal dementia. *FASEB J* 2010;**24**:4639–47.

108. Filiano AJ, Martens LH, Young AH, Warmus BA, Zhou P, Diaz-Ramirez G, *et al.* Dissociation of frontotemporal dementia-related deficits and neuroinflammation in progranulin haploinsufficient mice. *J Neurosci* 2013;**33**:5352–61.

109. Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. *Neuron* 2010;**68**:19–31.

110. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007;**69**:2197–204.

111. Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, *et al.* Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* 2008;**131**:2957–68.

112. Scherling CS, Hall T, Berisha F, Klepac K, Karydas A, Coppola G, *et al.* Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. *Ann Neurol* 2014;**75**:116–26.

113. Landqvist Waldö M, Frizell Santillo A, Passant U, Zetterberg H, Rosengren L, Nilsson C, *et al.* Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia. *BMC Neurol* 2013;**13**:54.

114. Whitwell JL, Weigand SD, Gunter JL, Boeve BF, Rademakers R, Baker M, *et al.* Trajectories of brain and hippocampal atrophy in FTD with mutations in *MAPT* or *GRN*. *Neurology* 2011;**77**:393–8.

115. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, *et al.* Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 2012;**367**:795–804.

Chapter 19

The family's perspective on FTD



Enduring the journey, a force for change

Susan Dickinson and Jill Shapira

Hodges' Frontotemporal Dementia, Second Edition, ed. Bradford C. Dickerson. Published by Cambridge University Press. © Cambridge University Press 2016.

Frontotemporal dementia (FTD) is a disease that steals what we value most in ourselves and those we love: the ability to communicate and share emotions with the people in our lives; the aspects of personality – our judgments, choices, and initiative – that make us the individuals we are; the capacity to understand nuanced humor, social rules and norms; and the ability to empathize and connect with our fellow human beings.

The “experts” in this condition are those who have been forced by fate to walk this path of loss, one step at a time. For the clinician who aspires to care for these families, to work with them to find effective treatments, palliative measures, and management techniques that will make a difference, an understanding of their journey to your door is instructive.

The family's journey

Mike and I met when we were freshmen in college. On our early dates we would walk through campus at night and talk for hours. I learned about his favorite philosophers, why he named his car Yahweh, and the latest atrocity he planned to peaceably protest. I remember I fell in love fast.

Looking back, we were an ambitious young couple. Married at 22, we juggled multiple jobs and took turns earning our masters degrees. We planned and plotted for a future bright with promise. While building for our future, Mike never forgot to focus on the present. Whether it was planning a date night, bringing home my favorite ice cream, or picking up a rose from the local gas station, he easily turned affection into action. Two weeks before our fifth wedding anniversary we found out that a baby was on the way.

It was during my pregnancy with our son that things began to change. I noticed that Mike was becoming socially withdrawn and he rarely wanted to talk. His behavior became erratic and unpredictable. He purchased things we couldn't afford, walked for miles in the middle of the night, and began having trouble meeting deadlines or following the dress code at work. The man who loved microbreweries and imported German beers was chugging Natty Ice in the shed to get drunk on weeknights. I started getting phone calls from Mike's friends wondering if he was "mad at them."

I became alarmed when Mike, a straight-A student who could translate philosophy texts in Hebrew, Greek, and Latin, failed his comprehensive exams for his Master's degree in Philosophy. It was around that time that I remember trying to make a grocery list with him and I noticed that he couldn't spell the word "rice" or remember the word for avocado.

By the time our son was six months old, Mike's executive functioning was so poor that I didn't feel comfortable leaving the two of them alone together. In September of 2008, I accompanied Mike to a routine physical appointment with his primary care physician. I asked her "my husband is acting so weird, does he have a brain tumor?" She was the first of eight medical and mental health professionals to misdiagnose him.

When we would go into appointments I would talk about changes and deficits in Mike's behavior. I said that he wasn't the same person, that his behavior didn't make sense. That he seemed apathetic. Mike said that I was a nag and that all his problems were because I had a baby and went back to work. I think that the professionals saw us as a couple with marital issues.

Mike saw two primary care physicians, three counselors, two psychiatrists, and one neurologist. He stayed overnight at the hospital and spent a week in a locked psychiatric unit. He had many tests. But, it wasn't until the ninth medical evaluation that he was properly diagnosed with FTD.

– Katie Brandt

Five years ago my wife Julia was a partner at a leading law firm in the city. She had a spotless reputation as being professional, productive, and she took particular pride in the personal connections she built with her clients. We had a good marriage, with two kids we both adored. We felt lucky, and happy.

But then things started to change. She had trouble getting out of bed in the morning, and seemed to lose enthusiasm for the cases and for her clients. She would start crying for no apparent reason. We would have a conversation and then five minutes later have the same conversation again. She actually told a neighbor that her new hair

color was ugly. The worst was the way she was with the kids, either ignoring them or snapping at them with no warning.

We went to the doctor, who diagnosed depression, and prescribed meds. But not much changed. We fought more and more frequently. I told her that her behavior wasn't acceptable. I kept asking why she was doing these things. Didn't she love us anymore? For some reason she just couldn't answer that. Something had changed, and my family started urging me to take the kids and leave.

Then she made a mistake at work with a key client. The senior partner at the firm insisted Julia go back to the doctor. This time we went to a neurologist, a memory disorder specialist who deals mostly with Alzheimer's patients and FTD patients. She passed all the tests that were given, but then the doctor said that the PET scan and MRI showed significant atrophy of both frontal and temporal lobes of Julia's brain. I know that Julia didn't believe what the doctor was telling us, but when it was made crystal clear that she would get fired and lose her long-term disability insurance, that got through. So, she agreed to retire, at 46 years old. Now she just sits around the house, eating and monopolizing the TV, not saying much to anyone unless we get in her way.

The reaction of friends and family has been really tough to deal with. Some people look at her and see a normal, healthy woman, and I know they think that Julia must be faking it. Others we just don't see any more, I guess it's easier for them to avoid the situation. The kids act this way sometimes, too. And I can't really blame them. When they ask what the future will bring, the only reassurance I can offer is that I love them, and somehow we'll make it through.

– Anonymous

If one interviews family members of a person with FTD, a picture of a convoluted and circuitous path to diagnosis emerges. Many of these stories contain common themes of confusion, isolation (from their loved one, from friends and family, from physicians and other medical professionals), and, often, a series of misdiagnoses. It is worth noting that it is often a specific crisis that propels the situation from one stage into the next. These crises may include financial mismanagement, loss of a job, emotional or physical conflict within the family, the affected individual putting him or herself into a harmful situation, or an arrest. [Figure 19.1](#) provides a schema of a common pattern that emerges, and notes the years that often accumulate as the family works their way to an accurate diagnosis.



Figure 19.1 The family's journey to a diagnosis of FTD.

Stage I. Something is wrong

Whether initial symptoms are word-finding difficulties, a change in energy level, a few lapses in judgment, or atypical or odd behavior, the earliest

changes are subtle and difficult to recognize. More to the point, when viewed in isolation or as an infrequent occurrence, all of these are things that any person might – and most of us do – experience occasionally. What person doesn't feel the need to be a couch potato once in a while? Indulge oneself with an impractical purchase? Forget a word? Make a decision that turns out to be imprudent? One of the greatest ironies of FTD is the fact that, as it begins to steal the very aspects of a person that make them the unique human being they are, it is that very uniqueness that masks the fact that something has begun to go wrong.

It is also a fact that many families, reflecting back in search of signs of when the disease began, discover that friends and co-workers noticed some of the earliest signs, but were reluctant to mention anything. Again, there is some irony in the fact that it is often informal social rules – we are reluctant to point out when a co-worker does something wrong or embarrassing; we don't want to insert ourselves into a marriage that may be having troubles – that prevent earlier recognition that there may, truly, be something wrong with a person we know.

After we shared the diagnosis of FTD with her co-workers, stories began to emerge, about mishandled clients, lost documents, and missed deadlines. No one had said anything at the time.

After my husband's diagnosis, two friends who I was estranged from came forward and shared nearly identical stories, about how he had made sexual overtures to each of them. Rather than tell me, they just disappeared from our lives.

I wish I had known at the time. Though it would have been painful, it would have been reassuring to know that I wasn't the only one who was noticing a change.

Stage II. Maybe there is a medical problem

At some point it occurs to someone – most often the spouse – that perhaps these strange changes in behavior are not willful, but rather that there may be a brain disorder. Occasionally it is the person him or herself who initiates the search for a cause for these incipient changes. But because the symptoms are fairly intangible, combined with the typical younger age of onset, and the fact that many general physicians, or even community neurologists and psychiatrists, are not familiar with FTD, often the family is sent home without a specific diagnosis.

I knew something was seriously wrong, but it was almost impossible to make other people understand the most troubling changes. They thought I was crazy.

Mom was complaining of word-finding problems, and there were increasing pauses in our phone conversations. How to explain that this didn't feel like a “normal” memory problem?

The doctor was hearing two different stories: Mine was one of bizarre changes, frustration, and confusion; his was one of a nagging wife, dissatisfied with midlife. Which of us would you believe?

I was several states away and couldn't seem to marshal the local resources to get Dad to a doctor who would understand what had changed.

Stage III. A series of medical professionals and opinions/diagnoses

Many marriages and other family relationships do not survive this far. Those that do face additional hurdles in this stage of the disease – one in which: individuals with the disease most likely do not recognize they have changed;

co-workers and friends who experience the symptoms may be reluctant to point them out and, instead, start to distance themselves; and medical professionals, practiced in diagnosis of psychiatric conditions or Alzheimer's disease, either conclude that there is no diagnosis or prescribe treatment for the wrong condition. It takes a tenacious caregiver, confident they know the affected person best, convinced there is something truly wrong, to keep making appointments, to keep telling their story, and to stay in the relationship.

It took three visits to our general practitioner before I could convince him that something was really wrong with Mary.

They tested for cognitive issues. They tested for memory. They did a brain scan, looking for tumors. But every test came back negative – there was nothing wrong.

I encouraged him to go to the doctor, who put him on meds for low testosterone. A few months later, with no relief from his strange behaviors, I encouraged him to go back and this time the doc said, “depression,” put him on meds, and said to come back in a year. I knew the year recheck wasn't right so I found a psychiatrist that he began seeing, who upped his depression meds. Still no improvement.

It took a year and a half to get Clark's diagnosis. The first five physicians that we went to had little or no knowledge of FTD. I myself have been an RN for seven years and I had never heard of FTD either.

Stage IV. Referral to a physician familiar with FTD

Certainly, not all families have such an extended path to the diagnosis. Some are lucky enough to have a family doctor who is familiar with the disorder; others live sufficiently near a major dementia center and referral to a medical team familiar with FTD occurs rapidly. Many others discover the diagnosis themselves, on the internet. But often this circuitous route to diagnosis has consumed the last, best years the patient and family have together.

June of last year his boss gave him a letter stating that if he didn't improve (his interpersonal skills, teamwork, follow-up, etc.) he was going to lose his job. This letter was an eye-opener because it confirmed that his behavior and personality changes were noticed outside of our home, as well. We went back to our GP, who finally referred us to a neurologist at a dementia center.

When I typed her list of symptoms for an internet search, up popped FTD. It was like fireworks going off: I went right down the page, checking off every feature listed on the website.

What a relief to find someone who understood what we were experiencing, and who could put a name to what was going on.

Stage V. The diagnosis is FTD

And so, having finally arrived at a diagnosis of FTD, where does this family find themselves? They are branded with a label they most likely have never heard of before, with little information as to the prognosis, course, and timeline ahead. They are told there are no disease-modifying treatments; there is no cure. Perhaps they are informed that the diagnosis remains

somewhat tentative, and will not be confirmed until autopsy. The only solid fact that can be presented to this family is how the journey will end.

The situation is daunting for clinicians as well. A primary goal of clinical medicine is cure or at least treatment to modify the disease progression. Yet at present, we still have no definitive drugs and few research treatment studies for FTD. We try medications developed for other disorders, or suggest non-pharmacologic behavior management strategies, but these techniques have received little systematic study. Unfortunately, owing to the complexities of reimbursement within today's healthcare system, clinicians are saddled with time constraints, making it difficult to develop individualized plans for patients and families. And yet, there *are* things you can do that will make a tremendous difference in the quality of this journey for yourself, for the family, and for the patient.

Managing the disease through partnership

The single most destructive aspect of FTD is the isolation it creates for the patient and family. At this point in the journey, despite the lack of approved treatments and definitive prognosis, the mere fact of a diagnosis can bring tremendous relief. Knowing there is a medical name for the symptoms is validation. The connection with a clinician or clinical team that understands the symptoms and their ramifications is comforting. And the realization that there is a broader community out there that has walked this path before brings affirmation and hope.

Despite the lack of traditional tools in a physician's armament when facing the task of managing a patient with FTD, the primary clinical care team has an opportunity to set a more positive tone from the start. Invite

family caregiver(s) to be full partners in any care plan. They are the ones who know the patient best and who are on the front line in terms of reporting troubling symptoms and disease progression. They are the ones who will implement any treatment strategy, and be able to report whether or not an intervention is having effect. Also, be open to the possibility that the patient him or herself may retain the insight and communication skills to play a role in setting treatment goals and strategy.

Building this partnership will necessarily entail listening carefully to what patients and caregivers say, helping them understand the disease process, and referring them for individualized assistance. Despite the lack of specific prognosis, there are themes to this journey with certain predictable factors and challenges the clinician can recognize. As our communal experience with FTD grows each year, there is an ever-expanding world of resources and strategies for the care team to employ. Working with patients, families, and clinicians, the Association for Frontotemporal Degeneration (AFTD) in the USA has developed guidelines to address many of these challenges, including steps to take after receiving an FTD diagnosis, ways to help young children and teenagers cope, and information about the genetics of FTD. A complete list of resources appears in the section Creating a broader community for resources and support, below.

Avoid nihilism after the diagnosis

As patients and families gradually realize FTD is a progressive condition and cannot be cured, they begin to alter their future plans. Clinicians, too, need to adjust their approach to manage behavioral, language, and other cognitive changes associated with FTD. Patients and families want and deserve an honest discussion of the current state of knowledge and lack of

treatment options, yet it is important to also communicate what *can* be done after delivering this distressing diagnosis. Families benefit greatly from a continued “emotional presence” from clinicians knowledgeable about the disease. This commitment prevents feelings of abandonment described by many families who receive the unhelpful message: “There is no treatment, no cure, and nothing more I can do.”

Identify a collaborative team

Facilitate the transition from diagnosis to management by identifying an appropriate care team. For example, specialized FTD programs in university-based settings may elect to coordinate all FTD-related care or may serve as consultants with patients’ primary care providers, speech therapists, nurses, and social workers by clearly documenting their assessments and recommended plans of care. Members of the treatment team then learn from experienced FTD clinicians through these consultations as they provide ongoing management within routine health management.

Families, too, are an integral part of the team, and appreciate clinicians who allow them roles as true partners by carefully attending to their observations as symptoms and behaviors evolve during the disease course. Since patients themselves generally do not recognize behavioral and cognitive changes caused by the illness, families seek ways to alert clinicians about these changes without making patients angry or causing them unnecessary grief. It is often helpful to speak with family members alone for a few minutes while patient vital signs are collected, or ask for a brief written description of observations and concerns. Finally, it can be difficult for family members to convince many FTD patients to agree to follow up with clinicians as they neither feel sick nor believe they have problems. Family feedback reveals that patients agree to appointments

because they like going to see their clinicians, particularly when clinicians and patients themselves forge a bond.

Recognize the impact of disrupted social relationships and obligations among younger individuals

Individuals with FTD develop difficulty sustaining their usual patterns of established interaction with family, friends, and colleagues. For example, characteristic features of behavioral variant FTD include culturally unacceptable alterations in social behavior, loss of emotional empathy, and apathy, while patients affected by language disturbance may be unable to understand and communicate with others in their network. The young age of onset and significant impact on social relationships distinguishes FTD from the more frequent late-onset Alzheimer's disease and underlies the relative lack of age-related services to the FTD population when compared with older individuals with dementing disorders. Additionally, loss of employment, career, and the prior daily structure can create a huge void in the patient's life.

Caregivers frequently report extreme difficulty maintaining social bonds with their loved ones because of dramatically changed personalities, decreased emotional empathy, and lack of social reciprocity among FTD patients. It is particularly challenging to find caregiver support groups or programs addressing their specific issues, including: younger age, dependent children, work responsibilities, and concomitant care of elderly parents in addition to a spouse with FTD.

Families with young children and teens struggle with the consequences of a parent's altered behavior and appreciate suggestions to help their offspring cope with their feelings. Many families go through role reversal between children and the diagnosed parent. Concern for their children is

heightened for families with a family history of FTD. The decision to obtain genetic information about a disease without treatment or cure requires careful discussion with clinicians. Referral to a genetic counselor is important before ordering genetic testing to help clarify important issues and concerns.

Suggest anticipatory legal and financial planning

People with FTD will eventually need someone to act on their behalf to make financial and healthcare decisions. Options range from powers of attorney and advance directives for healthcare to guardianship or conservator proceedings. All of these should be initiated as soon as the diagnosis is confirmed to permit the individual with FTD to participate in the process.

As previously discussed, FTD commonly affects younger working adults with bills, mortgages, and children for whom they are financially responsible. Patients risk job security because of either unacceptable workplace behaviors or inability to perform at previous levels; families may be unaware of these work-related issues until patients are fired. Suggest that families help patients draft letters to their human resource departments stating they are undergoing medical evaluation without listing symptoms or possible diagnoses; this action paves the way for retirement through disability (such as state and social security benefits) rather than employment termination owing to poor performance. It may be helpful to suggest consultation with an elder law or employment attorney to preserve benefits after becoming unable to work. Obtaining medical disability involves completing insurance forms to document the permanent and progressive nature of the disease. Because FTD is a rare condition, explicit

and detailed examples of why patients should no longer work may expedite approval.

In addition to the impact of FTD on patients' employment status, family members may suddenly find themselves needing to increase surveillance of patients unable to be left unsupervised owing to problem behaviors. This creates additional burdens on family members juggling work, home, and now caregiving responsibilities. Encourage these individuals to learn about their rights under the US Family and Medical Leave Act while mobilizing additional resources.

Assist with community placement

Finding appropriate community resources is a major challenge for FTD patients and their families. The vast majority of home-help organizations, day care centers, and assisted living and long-term care homes are targeted to seniors or those with memory problems associated with Alzheimer's disease. Staff at these facilities understandably worry about younger, physically healthy FTD patients with challenging behaviors and potential disruption to older clients. Families report greater success during the transition from home to institution when clinicians respond to facility concerns with detailed care plans and a willingness to promptly re-evaluate patients when requested. Families also need to be prepared to play the role of educator themselves, incorporating this new circle of professionals into the existing, collaborative care team. AFTD initiated the *Partners in FTD Care* program to develop best practices in community care. Quarterly electronic newsletters feature case studies of common FTD behaviors with detailed interventions. An online forum provides an opportunity for community professionals to receive personalized suggestions from experienced nurses and social workers for immediate problems.

Discuss research opportunities

Growing momentum in FTD basic and translational research is beginning to generate more opportunities for patients and their families to engage in clinical studies. The number of observational and interventional studies, and the infrastructure to support them, is expanding around the globe. Connecting your families to these opportunities can provide hope and bring meaning to their experiences. The National Institutes of Health (NIH) supports *clinicaltrials.gov*, a registry of clinical studies conducted globally.

Creating a broader community for resources and support

And so where does this journey leave the patient and caregiver? Many, certainly, are tapped out, drained by the constant need to explain, to guard, to care – all in extreme isolation, most of them by definition denied of the very person who had pledged to stand by them on life's journey, through sickness and health. And yet, others are motivated to *do* something. To help others understand their journey. To build new, more and better resources and information for the individuals and families that are following the path behind them. To somehow, some way, derive some good from the devastation of this disease.

AFTD was founded (as the Association for Frontotemporal Dementias) by one such caregiver. In 2002, Helen-Ann Comstock, convinced of the need for an organization dedicated specifically to improving the lives of families coping with FTD and advancing research into treatment and a cure, decided to create such an organization. She was soon joined by a handful of other dedicated volunteers who, like herself, had lost a spouse or close family member to this disease. Together they crafted the broad mission of the

organization, which incorporates elements of both caring for the patient and family *today* while stimulating research to build a more promising *tomorrow*. (See [Box 19.1](#))

Box 19.1

The Association for Frontotemporal Degeneration (AFTD) is a non-profit organization whose mission is to:

- Promote and fund **research** into finding the cause, therapies, and cures for frontotemporal degeneration
- Provide **information, education, and support** to persons diagnosed with an FTD disorder, and for their families and caregivers
- **Educate** physicians and allied health professionals about frontotemporal degeneration and how to improve patient care
- Bring about greater **public awareness** of the nature and prevalence of frontotemporal degeneration and the needs of those who are coping with it
- **Advocate** with public officials and promote public and private programs that provide appropriate, affordable, and high-quality, long-term health care and social services
- **Facilitate** the international exchange of ideas

Affirming our mission:

We envision a world where frontotemporal degeneration is understood, effectively diagnosed, treated, cured, and ultimately prevented.

Like all voluntary health organizations, AFTD's early years were fueled primarily by the commitment and hard work of families. Like all such organizations dedicated specifically to a rare disease, the hurdles of awareness and resources were daunting. One key factor that enabled AFTD to survive and grow was the commitment and passion demonstrated not just by the caregivers, but also by a key group of professional clinicians and researchers who understood this disease best. Founding members of AFTD's Medical Advisory Council (MAC) included leaders from across the USA and Canada who were generous with their time and expertise to guide and nurture the young organization. This is a tradition that continues, and from which AFTD still derives much of its authority and strength.

Also critical to the organization's ability to grow has been recognition that, as medicine and science advance our understanding of the FTD clinical syndromes and their underlying, shared pathologies and etiologies, so too must nomenclature and the very concept of whom this community comprises adapt. In order to succeed in its mission AFTD needs to pull together people with fairly disparate disease experiences (i.e., the journey of an individual with primary progressive aphasia (PPA) bears little in common with that of a behavioural variant (bvFTD) patient or a patient whose disease presents as a movement disorder), and who receive a variety of clinical diagnoses.

Another challenge concerns the need to broaden the definition of whom the organization represents. Just as the very concept of family at present has flexed, to include same-sex marriages, blended families, and stay-at-home dads, so too are we recognizing that the main caregiver for an FTD patient is not always a spouse. The primary caregiver not infrequently is an adult child or an aged parent, who may not live local to the patient. Still other patients, by virtue of the symptoms of the disease itself, find themselves alone, having to play the role of both patient and caregiver themselves.

Moreover, there is growing recognition that this disease has an impact on the entire family system, inflicting potential harm to everyone in its path. All of these perspectives are valid, and if the organization is to stay vibrant and mobilize a broad base to both fund and man the work ahead, all must be incorporated into the voice of AFTD.

At present the organization has emerged from its start-up phase, with a professional staff of 12 and a growing cadre of committed volunteers across the USA. Guided by a Board of Directors which has intimate knowledge of the family's journey, and aided by expert professionals both on the MAC and throughout the broader community, the organization creates novel resources and implements programs to specifically target the unique challenges faced by the family and clinical team. Some of these initiatives and resources are listed below.

It is important to note that many, if not most, of these initiatives are built upon the shoulders of and/or in partnership with larger, more well-established organizations and government institutions. The National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), the Alzheimer's Drug Discovery Foundation, the ALS Association, the Alzheimer's Association, CurePSP, and the National Aphasia Association are among these valuable partners. In recent years a handful of additional non-profit organizations joined AFTD in the USA to advocate for and fund the specific needs of the FTD community (most notably the Tau Consortium and the Bluefield Group, both created and funded by families touched by a subtype of FTD). Looking ahead, we are encouraged by increasing interest on the part of big pharma and biotechs, as well as by emergent resources and activity in other countries.

AFTD initiatives and programs

Promoting and funding research

Research grant programs. AFTD sponsors a small but growing research grant program that supports pilot projects in the laboratory and the clinic, a postdoctoral fellowship, and translational research.

FTLD NACC Module. The National Alzheimer's Coordinating Center supports a database of standardized longitudinal clinical data collected by the 29 specialty centers participating in the Alzheimer's Disease Research Centers Program. With support by NIA and NINDS, the AFTD played a key role in developing a supplementary module of common data elements specifically for FTD and PPA. This has resulted in a large and growing set of data, publicly available to investigators for analysis to assist in understanding the natural history of these conditions and for planning clinical trials.

Induced Pluripotent Stem (iPS) Cell Consortium. Funded by a public-private partnership and managed by NINDS, AFTD has been involved in developing this initiative to create iPS cells for Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and FTD, and making these cell lines available publicly as a vital resource to stimulate research.

Scientific meetings. AFTD has provided support for a host of meetings that stimulate novel partnerships to leverage some of the genetic and pathologic features FTD shares with ALS and Alzheimer's disease. Some of the most exciting work over the last two years has occurred around the *C9orf72* genetic mutation, now recognized as common in both familial ALS and FTD.

The FTD Treatment Study Group. Founded in collaboration with academic, government, non-profit, and industry partners, this group seeks to address the common hurdles to FTD drug development and testing.

Supporting and informing families

A HelpLine via toll-free phone and email (866-507-7222, info@theaftd.org). AFTD staff coordinate this resource and call upon years of accumulated knowledge to answer questions posed by patients, caregivers, and professionals and to connect them with local and national resources.

Respite and travel grants. These provide primary caregivers with the means to obtain short-term respite, and patients and family members with the means to attend educational conferences.

Telephone support groups. These programs are dedicated to specific challenges or sectors within our community; current groups address behavior symptoms, language symptoms, parents with children and teens, grief after a loved one dies, and persons who themselves are diagnosed.

Education of FTD support group leaders. At present there are more than 70 FTD support groups across the USA and Canada. This is a mixture of groups sponsored by clinics, the Alzheimer's Association, or operated independently by an individual. AFTD hosts quarterly webinars, each featuring an expert or experts who can address a specific, emergent challenge being reported by these leaders or through the HelpLine.

Educational conferences. AFTD hosts its own education conference each year at a different location in the USA. It also co-sponsors a growing number of regional conferences hosted by local organizations or clinics. In alternate years, AFTD co-sponsors the international conference on FTD and designs a full-day program for caregivers in conjunction with the research meeting.

www.theaftd.org. The AFTD website is a repository of medical and care management information on FTD. Clinics experienced with FTD, support groups, and other resources are listed by US region and by country.

Original publications. AFTD has created original material to address some of the most pressing challenges for our community, including booklets for persons facing a new diagnosis, for those concerned with the genetics of FTD, and for young families still raising children and teens.

Educating medical and healthcare professionals

Continuing medical education (CME) and non-CME courses. AFTD has partnered with organizations (e.g., the Department of Health and Human Services, the National Institutes of Health, the American Psychiatric Association, the American Speech-Language-Hearing Association, the National Adult Day Services Association, and the National Aphasia Association) to educate physicians and other health professionals about accurate diagnosis and appropriate treatment in FTD.

Partners in FTD Care. This AFTD initiative aims to educate community health professionals as to the special challenges in caring for an individual with FTD, with a goal of expanding access to services that are able to provide appropriate care for FTD families.

Promoting awareness

A growing volunteer network. Awareness is the key to everything this community needs to accomplish. In addition to an informative website, newsletters, Facebook, and Twitter, AFTD works through a growing network of volunteers across the country that delivers our materials and speaks about this rare disease to a wide array of audiences.

Putting a face on the disease. “It Is What It Is” is an 18-minute film, available online or as a DVD, that shares the stories of four families living with FTD. AFTD also works with families willing to tell their stories and

who, increasingly, are garnering local and national press coverage about this rare disease.

National FTD Awareness Week. In October 2013, AFTD sponsored the first annual FTD Awareness Week; volunteers in 26 US states and 5 Canadian provinces hosted 56 AFTD-branded “Food for Thought” events. This initiative is growing, with the First World FTD Awareness Week celebrated in 10 countries in 2015.

Advocating for support and research funding

NAPA. The National Alzheimer's Project Act, enacted by Congress in 2010, is designed to address the growing burden placed on our society by Alzheimer's disease and related dementias. AFTD staff and volunteers are working hard to ensure that the needs unique to our population, namely those driven by young onset and unusual presentation, are addressed by the plan. In 2013 AFTD joined NINDS and others in co-sponsoring an event at which experts identified research priorities for FTD and other non-Alzheimer dementias for inclusion in the national plan in 2015 and beyond.

State initiatives. Most recently, AFTD has crafted an “AFTD Guidance for State Alzheimer's Plans,” a document for volunteers to use as they advocate to ensure that the needs of the FTD community are addressed in the growing number of state Alzheimer's plans.

Facilitating international partnerships

Yet another promising trend is the creation of similar non-profit organizations around the globe. Non-profit groups specifically dedicated to FTD can be found in the UK, Australia, France, Italy, the Netherlands, and Argentina. In other countries similar activities are being nurtured within broader dementia groups or by local clinical experts. AFTD actively

mentors nascent groups in other countries and is very pleased to provide all of our materials for translation into other languages. Together this expanding group of organizations meets every other year at the International FTD Conference to encourage cross-border collaboration for research, support, awareness, and education. A current list of like-minded organizations around the world can be found at www.theaftd.org under “International Resources.”

A force for change

Looking to the future, it is clear that some of the most daunting challenges lie ahead. Although research is proceeding at a dramatic pace, as highlighted throughout this book, we still do not have definitive biomarkers for diagnosis, to measure disease progression, or to demonstrate clinical efficacy of candidate treatments. We do not have clear outcome measures for clinical trials. We do not have a complete understanding of the incidence and prevalence of the FTD disorders. For those currently living with the disease, there is much room for improvement in daily management, symptomatic treatments, and support mechanisms. Certainly, underlying all of these issues is a fundamental need for education and increased awareness. What we have learned is that professionals and families, government, pharma, and non-profits need to work together to address these challenges.

What can the individual clinician or researcher do to advance the cause? On a daily basis, listen to what your patient and their family members are telling you. Keep FTD on your list for differential diagnosis. Be familiar with the diagnostic criteria, and, if necessary, be ready to refer a patient to someone with more experience of making this diagnosis. Once a

diagnosis is made, know that despite the current lack of drugs there is an increasing array of resources and information on effective management strategies. Call upon AFTD and other sources to identify these strategies. Invite the primary caregiver(s) to be full partners in any care plan.

On a broader level, consider engaging with the various entities identified in this chapter to help build a more hopeful future. Consider participating in a clinical trial, or initiate a research project of your own. Speak at a local support group. Educate your peers about the fact that not all dementia is Alzheimer's, and it can occur at a young age and present with an unusual, unpredictable set of symptoms. There is an ever-growing community of people affected by FTD who are willing to provide the passion, the funding, and put a public face on these disorders. We invite and welcome your partnership.

After going through so much with Mike's illness, and knowing how difficult a struggle FTD can be, many people have asked me why I continue to involve myself in this terrible disease. I did not have the benefit of knowing about AFTD while Mike was alive, but joined a year after his passing. I did so because I wanted to give value to the journey, and share with others who are either currently experiencing this struggle or who are seeking to understand a loved one or friend the knowledge I gained.

What I learned is that knowledge is the best medicine you can have in the face of something so daunting, and if we who have been there on the front lines don't stay involved and educate and guide others, we sell ourselves short and rob them of important experience. We, as former caregivers, are their hope and their relief

and can help them navigate through the mountain of issues that arise every day.

Being a part of AFTD gave me purpose right after Mike's passing. Being a part of AFTD now gives me continued hope that I can help make a difference in someone else's struggle. Being a part of AFTD these many years after Mike's passing honors him and acknowledges that he was here and that his journey with FTD is not forgotten and may in some way make that burden lighter for someone else.

– Beth Walter

Index

A β peptides, CSF, [145–146](#) , [147](#)
acetylcholinesterase inhibitors, [37](#), [232–233](#) , [245](#)
activities of daily living (ADLs), [211–213](#)
 anatomical correlates, [221–222](#)
 basic, [211](#), [212](#)
 behavioral variant FTD, [213–214](#) , [215](#), [216](#), [220](#)
 cognitive and behavioral changes and, [214](#), [220–222](#)
 corticobasal degeneration, [220](#), [221](#)
 evaluation, [212](#)
 instrumental, [211–212](#)
 logopenic progressive aphasia, [219–220](#)
 management strategies, [223–224](#)
 progressive non-fluent aphasia, [217–218](#) , [219](#), [220](#)
 progressive supranuclear palsy, [220](#), [221](#)
 semantic dementia, [216–217](#) , [218](#), [219](#), [220](#)
Addenbrooke's Cognitive Examination (ACE), [99](#), [106–107](#)
Advanced Caregiver Training (ACT), [237](#)
affective disorders, differential diagnosis, [34–35](#)
age at presentation, [92](#)
aggression, [231–232](#) , [236–237](#)
agitation, [231–232](#) , [236–237](#)
agnosia
 associative, [4](#), [32](#)
 multimodal, semantic dementia, [20](#)
agrammatism, [18](#), [32](#), [57](#)
Akelaïtis variant frontotemporal dementia, [82](#)

- alien hand syndrome, [20](#)
- alkalizing drugs, [251](#)
- ALS. *See* [amyotrophic lateral sclerosis](#)
- Alzheimer, Alois, [2](#)
- Alzheimer's disease (AD)
 - clinicopathologic correlation, [23](#)
 - CSF biomarkers, [143](#), [146–147](#)
 - differential diagnosis, [23–24](#), [33–34](#)
 - frontal variant, [181](#)
 - imaging, [137](#)
 - tau protein, [84](#)
 - TDP-43 pathology, [176–177](#)
 - type pathology, logopenic progressive aphasia, [61–62](#)
- Alzheimer's Disease Research Centers Program, [269](#)
- Alzheimer's Prevention Initiative (API), [254](#)
- amiodarone, [251](#)
- amnesic aphasia, [1](#), [4](#)
- amyloid- β biomarkers, CSF, [145–146](#), [147](#)
- amyotrophic lateral sclerosis (ALS; motor neuron disease; MND)
 - frontotemporal cognitive-behavioral syndromes, [70](#)
 - FTD with. *See* [frontotemporal dementia-amyotrophic lateral sclerosis](#)
 - genetics, [190](#)
 - overlap with FTD, [8](#), [20–21](#), [68–69](#)
 - pathologic substrate, [7](#)
 - with behavioral impairment (ALSbi), [70](#)
 - with cognitive impairment (ALSci), [70](#)
- Amyotrophic Lateral Sclerosis Cognitive Behavioral Screen (ALS-CBS), [74](#)
- animal models, [197–206](#)
 - C9orf72* repeat expansion, [199](#)
 - CHMP2B* mutations, [206](#)
 - drug development, [252–254](#)
 - FTLD-TDP, [177](#), [204–205](#)
 - FUS proteinopathy, [180](#), [204–205](#)

- GRN mutations, [203](#), [253– 254](#)
- tauopathies (FTLD-tau), [171](#), [200](#), [201](#)
- VCP mutations, [205](#)
- anomia/naming deficits
 - imaging correlates, [138](#)
 - management, [232](#)
 - primary progressive aphasia, [18](#)
 - semantic dementia, [4](#), [19](#), [59](#)
- anterior cingulate atrophy, [125– 126](#) , [130](#)
- Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) studies, [254](#)
- antidepressants, [37](#), [231](#), [244– 245](#)
- anti-epileptics, [247](#)
- antipsychotics, [37](#), [231– 232](#) , [245– 246](#)
- antisense oligonucleotides (ASO), [252](#)
- apathy/inertia
 - behavioral variant FTD, [16](#), [31](#), [46](#)
 - case study, [38– 39](#)
 - differential diagnosis, [96](#), [97](#)
 - FTD-ALS, [8](#), [73](#)
 - imaging studies, [138](#)
 - management, [215](#), [232](#), [235](#)
- aphasia. *See also* [language disturbances](#)
 - amnesic, [1](#), [4](#)
 - Gogi, [4](#)
 - management, [232](#)
 - progressive
 - bvFTD, [17](#)
 - differential diagnosis, [24](#)
 - primary. *See* [primary progressive aphasia](#)
 - transcortical sensory, [4](#), [19](#)
- applause sign, [85](#)
- apraxia
 - corticobasal degeneration, [20](#)

management, [218](#)
 neuroanatomical correlates, [59](#)
 progressive non-fluent aphasia, [18](#), [57](#)
 apraxia of speech (AOS), [18](#), [32](#), [57](#)
 imaging studies, [138](#)
 arginine hypomethylation, FET proteins, [178](#), [180](#)
 argyrophilic grain disease (AGD), [169](#), [171](#)
 aripiprazole, [246](#)
 arterial spin labeling (ASL) perfusion imaging, [128](#)
 Association for Frontotemporal Degeneration (AFTD), [230](#), [265](#), [267– 268](#) ,
 [270](#)
 associative agnosia, [4](#), [32](#)
 astrocytes, tufted, [168](#)
 astrocytic plaques, [170](#)
 attention-deficit hyperactivity disorder (ADHD), [98](#)
 attentional tests, [107](#)
 atypical frontotemporal lobar degeneration with ubiquitin-positive pathology
 (atypical FTL-D-U), [22](#), [177](#), [178](#), [179](#)
 Auditory-Verbal Learning Test (AVLT), [108](#)
 augmentative and alternative communication devices (AACs), [234– 235](#)
 autism spectrum disorders (ASD), [98](#)
 autobiographical memory tests, [108– 109](#)
 autoimmune conditions, systemic, [251](#)
 Awareness of Social Inference Test – Revised (TASIT-R), [113– 114](#)

 backward digit span test, [110](#)
 basal ganglia disorders, degenerative, [95](#)
 basophilic inclusion body disease (BIBD), [22](#), [177](#), [179](#), [180](#)
 behavioral assessment. *See also* [neuropsychological testing](#)
 behavioral variant FTD, [47– 48](#)
 FTD-ALS, [73– 74](#)
 behavioral disturbances
 behavioral variant FTD, [16– 17](#) , [31](#), [45– 47](#)

FTD-ALS, [73](#)
 imaging studies, [137–138](#) , [139](#)
 impact on activities of daily living, [220–222](#)
 management, [223–224](#) , [231–232](#) , [235–237](#)
 primary progressive aphasia, [18](#)
 semantic dementia, [20](#), [32](#)
 behavioral variant frontotemporal dementia (bvFTD), [3](#), [44–51](#) , [92](#), [93–94](#)
 behavioral features, [16–17](#) , [31](#), [45–47](#)
 case studies, [38](#), [225–226](#)
 classification, [5–6](#)
 clinical presentation, [31–32](#)
 clinical syndrome, [16–18](#)
 clinicopathologic correlation, [17](#), [23](#)
 cognitive features, [31–32](#) , [48–49](#)
 diagnosis, [45](#), [229](#)
 differential diagnosis, [23–24](#) , [96](#)
 emotion, social cognition and decision-making, [50–51](#)
 functional disability, [213–214](#) , [215](#), [216](#), [220](#)
 imaging, [125–126](#) , [128](#), [130](#), [133](#)
 imaging–behavior correlations, [137–138](#)
 management, [234](#)
 measuring behavioral changes, [47–48](#)
 measuring cognition, [49](#)
 neuropsychological testing, [106–116](#)
 overlap with ALS/MND, [69](#)
 pathology, [7](#), [44](#), [181](#)
 phenocopies, [3](#), [25](#), [35](#), [94](#), [130](#)
 primary progressive aphasia vs., [133](#)
 prognosis, [102](#)
 biomarkers, cerebrospinal fluid (CSF), [101](#), [143–146](#) , [148](#), [255](#)
 bipolar disorder, differential diagnosis, [96](#)
 Boston Naming Test, [118](#)
 bromocriptine, [246](#), [247](#)

C9orf72 repeat expansion, [69](#), [188– 189](#) , [197– 199](#)
 animal models, [199](#)
 antisense oligonucleotides (ASO), [252](#)
 case history, [157– 158](#) , [159](#)
 clinical presentation, [187](#), [189](#)
 dipeptide repeat (DPR) pathology, [175– 176](#) , [188– 189](#)
 FTD-ALS, [8](#), [21](#), [77](#), [188](#)
 genetic testing, [161– 162](#)
 mutation frequency, [186](#)
 neuroimaging, [134](#)
 neuropathology, [175– 176](#) , [189](#)
 pathophysiology, [177](#), [188– 189](#) , [197– 198](#) , [199](#)
 primary progressive aphasia, [63](#)
 psychotic symptoms, [35](#), [73](#), [96](#)
 repeat length effects, [191](#)
 therapeutic targeting, [251– 252](#)
Caenorhabditis elegans, [171](#), [254](#)
 Cambridge Prospective Memory Test, [109](#)
 Cambridge Semantic Memory Battery, [117](#), [119](#)
 carbamazepine, [247](#)
 caregivers, [230– 231](#) . *See also* [family](#)
 as informants, [47– 48](#) , [98– 99](#)
 burden, [222](#), [223](#)
 clinician relationships, [230](#), [265– 267](#)
 education, [223](#), [224](#), [234](#)
 managing functional disability, [223– 224](#)
 support for, [36– 37](#) , [237– 238](#) , [267– 270](#)
 CBD. *See* [corticobasal degeneration](#)
 cerebrospinal fluid (CSF) biomarkers, [101](#), [143– 146](#) , [148](#), [255](#)
 cerebrovascular disease, [24– 25](#) , [34](#)
 children
 as carers, [223](#)
 of FTD patients, [236](#), [266](#)

- safety concerns, [236](#)
- CHMP2B* gene mutations, [7– 8](#) , [181](#), [189– 190](#)
 - mutation frequency, [186](#)
 - pathophysiology and animal models, [205– 206](#)
- cholinesterase inhibitors. *See* [acetylcholinesterase inhibitors](#)
- chromosome 17-linked disease. *See* [frontotemporal dementia with parkinsonism-17](#)
- chromosome 3-linked disease (FTD-3), [7– 8](#) , [181](#)
- citalopram, [244](#)
- classification, disease, [15– 16](#)
- clinical course, [35– 36](#) , [102](#)
- Clinical Dementia Rating Scale (CDR), [213](#)
- Clinical Dementia Rating Scale for Frontotemporal Dementia (CDR-FTD), [213](#)
- clinical presentations, [30– 40](#)
 - atypical, and differential diagnosis, [33– 35](#)
 - case studies, [38– 40](#)
 - classical, [31– 33](#)
 - imaging correlations, [137– 139](#)
- clinical syndromes, [16– 21](#) , [93– 94](#)
 - molecular correlates, [166](#), [181](#)
 - neuroimaging, [125– 133](#)
- clinical trials, [255](#), [267](#)
- clinicopathologic correlations, [23](#), [93](#)
- clomipramine, [244](#)
- clozapine, [231– 232](#)
- cognitive assessment. *See also* [neuropsychological testing](#)
 - behavioral variant FTD, [49](#)
 - FTD-ALS, [73– 74](#)
 - office-based, [99](#)
- cognitive deficits
 - behavioral variant FTD, [31– 32](#) , [48– 49](#)
 - FTD-ALS, [69– 70](#)
 - imaging correlations, [138](#)

- impact on functional ability, [214](#), [220– 222](#)
 - management, [232– 234](#)
- communication impairments. *See also* [language disturbances](#)
 - management, [218](#), [224](#), [234– 235](#)
- community care, [267](#)
- compulsive behaviors, [46– 47](#) , [96– 97](#)
 - imaging studies, [138](#)
 - management, [231](#), [232](#), [236](#)
- Conners' Continuous Performance Test (CPT), [107](#)
- constructional abilities, [49](#)
- continuity of care, [231](#)
- “Cookie Theft” picture, Boston Test, [120](#)
- corticobasal degeneration (CBD), [20](#), [82– 87](#)
 - biomarkers, [87](#)
 - clinical phenotypes, [84– 86](#)
 - clinicopathologic correlation, [23](#), [24](#)
 - diagnostic criteria, [85– 86](#)
 - functional disability, [220](#), [221](#)
 - genetics, [84](#)
 - imaging, [86– 87](#) , [137](#)
 - overlap with primary progressive aphasia, [18](#)
 - pathology, [22](#), [83– 84](#) , [169– 170](#)
 - pharmacotherapy, [233](#)
 - progressive non-fluent aphasia, [57](#), [58](#)
 - use of term, [20](#), [85](#)
- corticobasal degeneration syndrome (CBDS), [20](#), [82– 83](#)
- corticobasal syndrome (CBS), [8– 9](#) , [85– 86](#)
 - Alzheimer's disease pathology with, [24](#)
 - imaging, [86– 87](#)
 - PSP pathology with (PSP-CBS), [85](#)
 - use of term, [20](#), [85](#)
- corticodentatonigral degeneration with neuronal achromasia, [82](#)
- Creutzfeldt–Jakob disease (CJD), [25](#), [94](#)

- davunetide, [250](#), [254](#), [255](#)
- day programs, [237](#)
- decision-making deficits, [50](#)– [51](#)
- dementia of frontal type, [3](#), [15](#)
- dementia with Lewy bodies (DLB)
 - clinicopathologic correlation, [23](#)
 - differential diagnosis, [34](#)
 - imaging, [137](#)
 - TDP-43 pathology, [176](#)– [177](#)
- dementias, rapidly progressive (RPD), [94](#)– [95](#)
- demographics, disease, [92](#)
- depression
 - differential diagnosis, [34](#)– [35](#) , [96](#)
 - management, [237](#)
- dextroamphetamine, [246](#)
- diagnosis, [229](#)– [230](#)
 - family's journey, [262](#)– [265](#)
 - longitudinal reassessment, [102](#)
 - management after, [265](#)– [267](#)
 - methods, [98](#)– [101](#)
 - recommended terminology, [102](#)
- dietary preferences, altered. *See* [eating behavior](#)
- differential diagnosis, [23](#)– [25](#) , [33](#)– [35](#) , [94](#)– [98](#)
- diffusion tensor imaging (DTI)
 - behavioral variant FTD, [127](#)
 - FTD-ALS, [74](#)– [76](#) , [130](#)
 - genetic FTD syndromes, [135](#)
 - logopenic progressive aphasia, [133](#)
 - progressive non-fluent aphasia, [59](#), [133](#)
 - semantic dementia, [132](#)
- Digit Span Forward test, [107](#)
- dipeptide repeat (DPR) protein pathology, [175](#)– [176](#) , [188](#)– [189](#)
- disability, functional. *See* [functional disability](#)

disease-modifying treatments, potential, [248– 254](#)

disinhibition

- behavioral variant FTD, [16](#), [31](#), [45– 46](#)
- case study, [38](#)
- imaging studies, [138](#)
- impact on daily life, [217](#)
- management, [218](#), [231– 232](#) , [235– 236](#)

D-KEFS (Delis–Kaplan Executive Function System), [112](#)

Dominantly Inherited Alzheimer's Network (DIAN), [254](#)

donepezil, [245](#)

dopamine augmentation therapies, [233](#), [246– 247](#) , [248](#)

dressing, [215– 216](#) , [219](#)

driving, [214](#), [215](#), [217– 218](#) , [219](#)

Drosophila melanogaster, [171](#), [198](#), [254](#)

dual-task impairments, [71](#), [76](#)

dysexecutive syndrome. *See* [executive dysfunction](#)

dyslexia

- phonologic, [138](#)
- surface, [138](#)

dystonia, management, [232](#)

dystrophic neurites (DN), [172](#), [173](#)

- familial FTLD-TDP, [175](#), [176](#)
- FET-positive, [178](#)
- FTLD-TDP subtypes, [174](#), [175](#)

eating behavior

- behavioral variant FTD, [31](#), [38](#), [47](#), [216](#)
- imaging studies, [138](#)
- management, [216](#), [219](#), [232](#), [236](#)
- semantic dementia, [217](#)

Edinburgh Cognitive and Behavioural ALS Screen (ECAS), [74](#), [75](#)

education

- carer, [223](#), [224](#), [234](#)

healthcare professionals, [270](#)
 electroencephalography (EEG), [100](#)
 electromyography, [101](#)
 Emotional Morphing Test, [114](#)
 emotional processing deficits
 behavioral variant FTD, [50](#)
 FTD-ALS, [72–73](#)
 imaging studies, [139](#)
 testing, [113–114](#)
 empathy, loss of, [31](#), [46](#)
 imaging studies, [138](#)
 management, [236](#)
 employment, [267](#)
 environmental modifications, [223–224](#), [235](#)
 epidemiology, [30–31](#)
 epothilone D, [250](#)
 EWS (Ewing's sarcoma) protein, [177](#), [178](#), [179](#), [180](#)
 Executive and Social Cognition Battery (ESCB), [115](#)
 executive dysfunction
 behavioral variant FTD, [5](#), [16–17](#), [31](#), [48–49](#)
 FTD-ALS, [70–71](#)
 imaging studies, [138](#), [139](#)
 management, [215](#), [232](#), [233–234](#)
 testing, [110–112](#)
 extrapyramidal symptoms. *See* [parkinsonism/extrapyramidal symptoms](#)

 Face task, [112](#)
 Face–Place Test, [109–110](#)
 falls, [84–85](#), [231](#), [232](#), [235](#)
 familial frontotemporal dementia. *See also* [genetics](#)
 FTDP-17. *See* [frontotemporal dementia with parkinsonism-17](#)
 imaging, [134–136](#)
 primary progressive aphasia, [62–63](#)

secondary prevention, [255](#)
 TDP-43 proteinopathies, [175– 176](#)
 family, [262– 271](#) . *See also* [caregivers](#)
 discussing pathology results, [239](#)
 impact of genetic testing, [161](#), [162](#)
 journey to diagnosis, [262– 265](#)
 managing after diagnosis, [265– 267](#)
 resources and support, [267– 270](#)
 family history, [156](#)
 Faux Pas Test, [112](#)
 FET (FUS/EWS/TAF15) proteins, [177](#)
 arginine hypomethylation, [178](#), [180](#)
 in disease, [178](#)
 other neurodegenerative diseases, [180](#)
 pathophysiology, [180](#)
 positive FTL. *See* [frontotemporal lobar degeneration with FET pathology](#)
 finances, managing own, [214– 215](#) , [218](#), [219](#)
 financial planning, anticipatory, [266– 267](#)
 first- and second-order belief tasks, [112](#)
 [¹⁸F]-fluorodeoxyglucose positron emission tomography (FDG-PET)
 behavioral variant FTD, [129– 130](#)
 FTD-ALS, [74](#)
 logopenic progressive aphasia, [61– 62](#) , [63](#)
 fluoxetine, [244](#)
 fluvoxamine, [244](#)
 Food and Drug Administration (FDA), [243](#), [255](#)
 food preferences, altered. *See* [eating behavior](#)
 footbridge dilemma, [50](#)
 fractional anisotropy (FA)
 behavioral variant FTD, [127](#)
 FTD-ALS, [74– 76](#)
 progressive non-fluent aphasia, [133](#)
 semantic dementia, [132](#)

Free and Cued Selective Reminding Test (FCSRT), [108](#)

Frontal Assessment Battery (FAB), [99](#), [110](#)

Frontal Behavioral Inventory (FBI), [18](#), [99](#)

frontal degeneration of non-Alzheimer type, [2–3](#)

frontal lobe atrophy

- behavioral variant FTD, [6](#), [125–126](#), [127](#), [128](#)
- FTD-ALS, [130](#), [131](#)
- semantic dementia, [6](#), [130](#)

frontal screening tools, [110](#)

frontal variant frontotemporal dementia. *See* [behavioral variant frontotemporal dementia](#)

frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS), [8](#), [20–21](#), [68–77](#)

- assessing cognitive and behavioral change, [73–74](#)
- behavior change, [73](#)
- brain imaging, [130](#), [131](#)
- brain imaging and cognition, [74–76](#)
- case study, [40](#)
- cognitive change, [69–70](#)
- evolution of concept, [68–69](#)
- genetics, [8](#), [21](#), [77](#), [188](#), [190](#)
- management, [233](#), [234](#)
- pathology, [22](#), [76–77](#), [181](#)
- psychiatric symptoms, [20–21](#), [73](#)

Frontotemporal Dementia Behavioural Rating Scale (FTDFRS), [213](#)

frontotemporal dementia (FTD)

- behavioral variant. *See* [behavioral variant frontotemporal dementia](#)
- overlap syndromes, [8–9](#)
- terminology, [5–7](#), [16](#), [91](#), [92](#)

frontotemporal dementia linked to chromosome 3 (FTD-3), [7–8](#), [181](#)

frontotemporal dementia-motor neuron disease (FTD-MND). *See* [frontotemporal dementia-amyotrophic lateral sclerosis](#)

frontotemporal dementia (FTD) spectrum diseases, [16–26](#)

- abbreviations and acronyms, [16](#)
- clinical approach to diagnosis, [91– 102](#)
- clinical characteristics, [92– 93](#)
- clinical syndromes, [16– 21](#) , [93– 94](#)
- clinicopathologic correlations, [23](#), [93](#)
- CSF biomarkers, [143– 148](#)
- diagnostic assessment, [98– 101](#)
- differential diagnosis, [23– 25](#) , [33– 35](#) , [94– 98](#)
- historical aspects, [1– 8](#) , [15](#)
- pathology and molecular genetics, [21– 23](#)
- terminology, [2– 3](#) , [5– 7](#) , [15– 16](#) , [91](#), [92](#)
- uncommon clinical phenotypes, [94](#)
- frontotemporal dementia with parkinsonism-17 (FTDP-17), [7– 8](#)
 - molecular genetics, [185– 186](#) , [187](#)
 - pathology, [169](#), [170](#)
 - pharmacologic therapy, [245](#), [248](#)
- frontotemporal lobar degeneration (FTLD), [5– 7](#) , [16](#), [165](#)
 - clinicopathologic relationships, [93](#)
 - molecular classification, [166](#)
 - use of term, [92](#)
- frontotemporal lobar degeneration with FET pathology (FTLD-FET; FUS proteinopathies), [6](#), [22](#), [177– 180](#)
 - imaging, [137](#)
 - pathogenesis, [180](#), [200– 203](#)
 - pathologic features, [178](#), [179](#)
 - pathologic subtypes, [166](#), [178– 180](#)
- frontotemporal lobar degeneration with FUS pathology. *See* [frontotemporal lobar degeneration with FET pathology](#)
- frontotemporal lobar degeneration with no inclusions (FTLD-ni), [166](#), [181](#)
- frontotemporal lobar degeneration with tau-positive inclusions (FTLD-T; FTLD-tau; tauopathies), [6](#), [22](#), [165– 171](#)
 - corticobasal degeneration, [83– 84](#) , [169](#)
 - familial, [7](#)

FTD and parkinsonism (FTDP-17 *MAPT*), [170](#)
 globular glial tauopathies, [170](#)
 imaging studies, [137](#)
 models and pathophysiology, [171](#), [199– 200](#) , [201](#)
 molecular pathology, [186– 187](#)
 pathologic features, [166– 167](#) , [168](#)
 pathologic subtypes, [22](#), [166](#), [168– 169](#) , [171](#)
 Pick's disease, [168](#)
 potential therapies, [248– 250](#)
 prognostic value, [102](#)
 progressive supranuclear palsy, [83– 84](#) , [168– 169](#)
 frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP), [6](#), [22](#),
 [171– 176](#)
 familial, [175– 176](#)
 FTD-ALS, [76](#)
 imaging studies, [137](#)
 pathogenesis, [177](#), [200– 203](#)
 pathologic features, [172](#), [173](#)
 pathologic subtypes, [166](#), [172– 174](#) , [176](#)
 potential treatments, [250](#)
 type A, [174– 175](#)
 type B, [174](#), [175](#)
 type C, [174](#), [175](#)
 type D, [174](#), [175](#)
 frontotemporal lobar degeneration with ubiquitin-positive pathology (FTLD-U),
 [22](#)
 atypical, [22](#), [177](#), [178](#), [179](#)
 FTD-ALS, [76](#)
 imaging, [134– 135](#)
 subtypes, [22](#)
 frontotemporal lobar degeneration with ubiquitin proteasome system-positive
 pathology (FTLD-UPS), [166](#), [180– 181](#)
 FTD. See [frontotemporal dementia](#)

FTD Treatment Study Group, [269](#)

FTDP-17. *See* [frontotemporal dementia with parkinsonism-17](#)

FTLD. *See* [frontotemporal lobar degeneration](#)

functional disability, [211](#)

- anatomical correlates, [221](#)– [222](#)
- assessment, [212](#), [213](#)
- behavioral variant FTD, [213](#)– [214](#) , [215](#), [216](#), [220](#)
- carer burden, [222](#), [223](#)
- case studies, [225](#)– [226](#)
- cognitive and behavioral changes and, [214](#), [220](#)– [222](#)
- corticobasal degeneration, [220](#), [221](#)
- logopenic progressive aphasia, [219](#)– [220](#)
- management, [223](#)– [224](#) , [230](#)– [231](#)
- patterns and progression, [213](#)
- progressive non-fluent aphasia, [217](#)– [218](#) , [219](#), [220](#)
- progressive supranuclear palsy, [220](#), [221](#)
- semantic dementia, [216](#)– [217](#) , [218](#), [219](#), [220](#)

functional magnetic resonance imaging (fMRI; rsfMRI)

- behavioral variant FTD, [127](#)– [128](#) , [129](#)
- FTD-ALS, [74](#)
- genetic FTD syndromes, [135](#)– [136](#)

FUS (fused in sarcoma) protein, [177](#), [178](#), [200](#)– [203](#)

- FTD-ALS, [76](#)
- pathophysiology, [180](#), [202](#), [203](#)– [204](#)
- positive inclusions, [178](#), [179](#)

FUS gene mutations, [180](#), [186](#), [190](#)

FUS proteinopathies. *See* [frontotemporal lobar degeneration with FET pathology](#)

galantamine, [37](#), [245](#)

genetic counseling, [153](#)– [163](#)

Genetic Frontotemporal dementia Initiative (GENFI), [255](#)

Genetic Information Non-discrimination Act (GINA), [158](#)

- genetic testing, [154](#), [155](#), [157– 159](#)
 - impact on families, [161](#), [162](#)
 - interpreting results, [161– 162](#)
 - predictive, [157– 159](#) , [161](#), [162– 163](#)
- genetics, [22– 23](#) , [185– 186](#) , [192](#)
 - Mendelian genes, [185– 190](#)
 - pathologic correlations, [21](#)
 - primary progressive aphasia, [62– 63](#)
 - susceptibility genes and risk loci, [190– 191](#)
- genome-wide association studies (GWAS), [190](#), [191](#)
- glial cytoplasmic inclusions (GCI), [172](#), [173](#), [174– 175](#)
- globular glial inclusions (GGI), [169](#), [170](#)
- globular glial tauopathies (GGT), [169](#), [170](#)
- glycogen synthase kinase 3 (GSK3), [147](#), [249](#)
- Gogi aphasia, [4](#)
- G-quadruplex structures, [197– 198](#)
- Graded Faces Test (GFT), [109](#)
- grains, argyrophilic, [169](#), [171](#)
- granulin peptides (GRN), [144](#), [187](#), [201](#)
- GRN* gene mutations, [187– 188](#) , [200– 203](#)
 - animal models, [203](#), [253– 254](#)
 - case history, [154– 155](#)
 - clinical presentation, [94](#), [187– 188](#)
 - CSF progranulin levels, [144](#)
 - discovery, [7](#)
 - mutation frequency, [186](#)
 - neuroimaging, [133](#), [134– 136](#)
 - neuropathology, [175](#), [187](#)
 - pathophysiology, [177](#), [201– 203](#)
 - primary progressive aphasia, [62– 63](#)
 - serum progranulin levels, [144](#)
- GRN* gene variants, [191](#)

Hayling and Brixton test, [111– 112](#)
 healthcare professionals, education, [270](#)
 hereditary diffuse leukoencephalopathy with spheroids, [181](#)
 historical perspectives, [1– 8](#) , [15](#)
 history taking, clinical, [98– 99](#)
 hoarding disorder, [97](#)
 Holiday Apartment Task, [71](#)
 hospice care, [239](#)
 Hotel Task, [114](#)
 household chores, [215](#), [217](#), [218](#), [219](#)
 hummingbird sign, [86](#)
 Huntington's disease, [95](#), [180](#)
 hygiene, personal, [215– 216](#) , [217](#), [219](#)
 hyperorality, [17](#), [47](#). *See also* [eating behavior](#)
 hyperthyroidism, [99](#)

 imaging, [125– 139](#)
 clinical correlations, [137– 139](#)
 clinical syndromes, [125– 133](#)
 clinical trials, [255](#)
 comparative studies, [133](#)
 diagnostic evaluation, [100– 101](#)
 functional disability and, [221– 222](#)
 genetic syndromes, [134– 136](#)
 other neurodegenerative disorders, [137](#)
 pathologic syndromes, [137](#)
 immunotherapies, [249– 250](#)
 impulsive behavior, management, [232](#), [235– 236](#)
 inclusion body myopathy, Paget's disease of bone and frontotemporal dementia
 (IBMPFD), [176](#), [189](#), [205](#)
 incontinence, [216](#), [219](#)
 induced pluripotent stem cells (iPS), [253](#), [269](#)
 Ineco Frontal Screening (IFS), [110](#)

inertia. *See* [apathy/inertia](#)
 inflammation, [201](#)– [203](#) , [251](#)
 insular atrophy, [125](#)– [126](#) , [130](#)
 International Behavioral Variant Frontotemporal Dementia Criteria Consortium (FTDC), [45](#)
 international support groups, [270](#)
 α -internexin, [178](#)– [179](#) , [180](#)
 Interpersonal Reactivity Index (IRI), [114](#)
 intranuclear inclusion body disease, [180](#)
 Iowa Gambling Task (IGT), [50](#), [71](#), [114](#)– [115](#)

 Kissing and Dancing Test (KDT), [117](#)
 Kluver–Bucy syndrome, similarities to, [17](#), [47](#)

 language disturbances, [18](#). *See also* [aphasia](#)
 FTD-ALS, [71](#)– [72](#)
 imaging correlates, [138](#)
 management, [232](#), [234](#)– [235](#)
 progressive non-fluent aphasia, [32](#)– [33](#)
 testing, [56](#), [115](#)– [116](#)
 legal planning, anticipatory, [266](#)– [267](#)
 leisure activities, [217](#), [218](#), [235](#)
 letter fluency deficits. *See* [phonemic fluency deficits](#)
 Letters and Numbers Test, [110](#)
 levodopa, [233](#), [248](#)
 lipid-storage disorders, [95](#)
 lithium, [233](#), [249](#)
 LMTx (methylene blue), [249](#)
 logopenic progressive aphasia (LPA; lvPPA), [20](#), [61](#)– [62](#) , [92](#)
 behavioral variant FTD vs., [133](#)
 clinical presentation, [33](#)
 core differential features, [61](#)
 differential diagnosis, [62](#)

- functional disability, [219– 220](#)
- genetics, [62– 63](#)
- historical aspects, [4](#)
- imaging, [61– 62](#) , [133](#), [135](#)
- imaging–clinical correlations, [138– 139](#)
- neuropsychological testing, [117– 120](#)
- pathology, [61– 62](#) , [63](#)

magnetic resonance imaging (MRI), [125](#)

- behavioral variant FTD, [125– 126](#) , [128](#)
- clinical trials, [255](#)
- diagnostic assessment, [100](#), [101](#)
- FTD-ALS, [74– 76](#) , [130](#), [131](#)
- functional. *See* [functional magnetic resonance imaging](#)
- genetic FTD syndromes, [134– 136](#)
- logopenic progressive aphasia, [61](#), [62](#), [133](#), [135](#)
- progressive non-fluent aphasia, [101](#), [132– 133](#) , [134](#)
- semantic dementia, [130– 132](#)

management, [36– 37](#) , [229– 238](#) , [239](#)

- advanced stages, [238– 239](#)
- functional disability, [223– 224](#)
- initial/early stage, [229– 230](#) , [265– 267](#)
- middle stage, [230– 238](#)
- non-pharmacologic, [233– 238](#)
- pharmacologic. *See* [pharmacologic therapy](#)

mania, differential diagnosis, [96](#)

MAPT gene, [166](#), [167](#)

- variants, [191](#)

MAPT (tau) mutations, [167](#), [168](#), [185– 187](#)

- case history, [160– 161](#)
- clinical presentation, [187](#)
- corticobasal degeneration, [84](#)
- historical aspects, [2](#), [7](#)

mouse models, [253](#)
mutation frequency, [186](#)
neuroimaging, [134](#), [135](#)– [136](#)
neuropathology, [169](#), [170](#), [186](#)– [187](#)
pathophysiology, [199](#)– [200](#)
primary progressive aphasia, [62](#)
progressive supranuclear palsy, [84](#)
meal preparation, [215](#), [217](#), [218](#), [219](#)
Medication Scheduling Task, [71](#)
medications, managing own, [215](#), [217](#)
memantine, [37](#), [233](#), [247](#)– [248](#)
memory function
 behavioral variant FTD, [49](#), [107](#)– [108](#)
 imaging studies, [138](#)
 semantic dementia, [19](#)
 testing, [107](#)– [109](#)
Mendelian genes, [185](#)– [190](#)
methylene blue, [249](#)
methylphenidate, [233](#), [246](#)– [247](#)
microtubule-associated tau protein (*MAPT*). *See* [tau](#)
microtubule-stabilizing agents, [250](#)
Mind in the Eyes Test, [112](#)
Mind in the Voice Test, [112](#)
Mini-Mental State Examination (MMSE), [17](#)– [18](#) , [99](#), [106](#)
mitochondrial disorders, [95](#)
molecular pathology subtypes, [21](#), [22](#)– [23](#) , [166](#)
monoclonal antibodies, anti-tau, [249](#)– [250](#)
Montreal Cognitive Assessment (MOCA), [99](#)
motor neuron disease (MND). *See* [amyotrophic lateral sclerosis](#)
motor neuron disease inclusion dementia (MNDID), [21](#)
motor neuron disease type inclusions (MNDI), [22](#)
motor symptoms. *See also* [parkinsonism/extrapyramidal symptoms](#)
 management, [232](#), [233](#), [235](#)

mouse models, [253– 254](#) . *See also* [transgenic mouse models](#)

MRI. *See* [magnetic resonance imaging](#)

multidisciplinary management, [238](#)

Multiple Errands Test Hospital Version (MET-HV), [114](#)

multiple system tauopathy with dementia, sporadic, [170](#)

mutism, [18– 19](#) , [21](#), [72](#)

imaging studies, [138](#)

naming deficits. *See* [anomia/naming deficits](#)

naming tests, [118](#)

Nasu–Hakola disease, [181](#)

National Alzheimer's Coordinating Center (NACC), [269](#)

National Alzheimer's Project Act (NAPA), [270](#)

neurodegenerative diseases, other

differential diagnosis, [33– 34](#)

FET proteins, [180](#)

imaging studies, [137](#)

overlap with, [30](#)

rare frontal variants, [181](#)

TDP-43 pathology, [176– 177](#)

neurofibrillary tangle (NFT)-dementia, [169](#), [171](#)

neurofibrillary tangles (NFT), [84](#)

progressive supranuclear palsy, [168](#)

transgenic mouse models, [200](#), [201](#)

neurofilaments

CSF, [146](#), [147](#), [255](#)

immunoreactive inclusions, [178– 179](#) , [180](#)

neuroimaging. *See* [imaging](#)

neurologic disorders, differential diagnosis, [94– 95](#)

neurologic examination, [100](#)

neurologic signs, behavioral variant FTD, [32](#)

neuronal cytoplasmic inclusions (NCI), [172](#), [173](#)

dipeptide repeat (DPR) protein-positive, [176](#)

familial FTLD-TDP, [175](#), [176](#)
 FTLD-FET, [178](#), [179](#)– [180](#)
 FTLD-TDP subtypes, [174](#), [175](#)
 neuronal intermediate filament inclusion disease (NIFID), [22](#), [177](#), [178](#)– [179](#) ,
[180](#)
 neuronal intermediate filaments. *See* [neurofilaments](#)
 neuronal intranuclear inclusions (NII), [172](#), [173](#)
 dipeptide repeat (DPR) protein-positive, [176](#)
 familial FTLD-TDP, [175](#), [176](#)
 FTLD-FET subtypes, [178](#), [179](#)– [180](#)
 FTLD-TDP subtypes, [174](#), [175](#)
 other neurodegenerative diseases, [180](#)
 neurons, swollen achromatic, [22](#), [170](#)
 neuropathology, [6](#)– [7](#) , [21](#)– [22](#) , [165](#)– [182](#)
 discussion with family, [239](#)
 imaging studies, [137](#)
 molecular classification, [166](#), [181](#)
 Neuropsychiatric Inventory (NPI), [99](#), [255](#)
 neuropsychological testing, [100](#), [106](#)– [120](#) . *See also* [cognitive assessment](#)
 behavioral variant FTD, [106](#)– [116](#)
 primary progressive aphasia, [56](#)– [57](#) , [117](#)– [120](#)
 nihilism, avoiding, [266](#)
 nimodipine, [251](#)
 NMDA receptor antagonists. *See* [memantine](#)
 non-fluent variant primary progressive aphasia. *See* [progressive non-fluent aphasia](#)
 non-pharmacologic interventions, [233](#)– [238](#)
 normal pressure hydrocephalus (NPH), [95](#)
 Northwestern Anagram Test, [56](#)

 obsessive–compulsive disorder (OCD), [96](#)– [97](#)
 olanzapine, [231](#), [246](#)
OPTN gene mutations, [69](#), [77](#)

oral speech production test, [120](#)
oxytocin, [37](#), [233](#)

paclitaxel, [250](#)

Paired Associate Learning Test (PAL), computerized, [108](#)

palliative care, [239](#)

parkinsonism/extrapyramidal symptoms
 chromosome 17-linked. *See* [frontotemporal dementia with parkinsonism-17](#)
 corticobasal degeneration, [20](#)
 FTD with, [82](#), [83](#)
 management, [232](#), [248](#)
 progressive supranuclear palsy with (PSP-P), [85](#)

paroxetine, [37](#), [244](#)

pathology. *See* [neuropathology](#)

pathophysiology, [197](#)– [206](#)

pedigrees
 eliciting, [156](#)
 example, [155](#), [158](#), [160](#)

penguin sign, [86](#)

perseverative behaviors, [46](#)– [47](#) , [85](#)
 management, [232](#), [236](#)

PET. *See* [positron emission tomography](#)

pharmaceutical industry, [254](#)

pharmacologic therapy, [243](#)– [256](#)
 disease-modifying treatments, [248](#)– [254](#)
 future directions, [254](#)– [255](#)
 models for drug development, [252](#)– [254](#)
 symptomatic treatment, [37](#), [231](#)– [232](#) , [233](#), [243](#)– [248](#)

phenocopy cases, behavioral variant FTD, [3](#), [25](#), [35](#), [94](#), [130](#)

phonemic (or letter) fluency deficits
 behavioral variant FTD, [48](#)
 FTD-ALS, [70](#)– [71](#)
 logopenic progressive aphasia, [61](#)

phonologic errors, [61](#)

phosphorylated tau (P-tau), [145](#), [167](#), [199](#)
as therapeutic target, [248](#), [249](#)
CSF levels, [145](#), [146](#)

Pick, Arnold, [1– 2](#) , [15](#)

Pick bodies, [2](#), [6](#), [22](#), [168](#), [169](#)

Pick cells, [2](#), [22](#), [168](#)

Pick complex, [6](#), [16](#). *See also* [frontotemporal dementia \(FTD\) spectrum diseases](#)

Pick type A pathology, [22](#)

Pick type B pathology, [22](#). *See also* [corticobasal degeneration](#)

Pick type C pathology, [22](#)

Pick's disease (PiD), [1– 2](#) , [15](#), [82](#)
imaging, [137](#)
pathology, [168](#), [169](#)
use of term, [16](#)

pigmented orthochromatic leukodystrophy, [181](#)

Pittsburgh compound B (PiB) positron emission tomography (PET)
behavioral variant FTD, [130](#)
logopenic progressive aphasia, [4](#), [61– 62](#) , [133](#)
progressive non-fluent aphasia, [101](#)

pluripotent stem cells, induced (iPS), [253](#), [269](#)

poly-(glycine-proline) peptides, [252](#)

positron emission tomography (PET), [100– 101](#) , [125](#), [255](#)
behavioral variant FTD, [128– 130](#)
logopenic progressive aphasia, [61– 62](#) , [63](#)
progressive non-fluent aphasia, [101](#)

predictive genetic testing, [157– 159](#) , [161](#), [162– 163](#)

presenilin 1 (*PSEN1*) gene mutations, [24](#), [33](#)

primary lateral sclerosis (PLS), [69](#)

primary progressive aphasia (PPA), [3– 5](#) , [55– 64](#)
atypical/mixed cases, [62](#)
behavioral variant FTD vs., [133](#)

- classification, [5– 6](#)
- clinical syndromes, [18– 19](#)
- clinicopathologic correlation, [19](#), [23](#)
- diagnosis, [55](#), [229](#)
- differential diagnosis, [24](#), [33– 34](#)
- genetic studies, [62– 63](#)
- imaging, [130– 133](#)
- imaging–clinical correlations, [138– 139](#)
- logopenic/phonologic variant. *See* [logopenic progressive aphasia](#)
- management, [63– 64](#) , [230](#), [234– 235](#)
- neuropsychological testing, [56– 57](#) , [117– 120](#)
- non-fluent/agrammatic variant. *See* [progressive non-fluent aphasia](#)
- prognosis, [102](#)
- semantic variant. *See* [semantic dementia](#)
- use of term, [91](#), [92](#)
- variants, [57– 61](#) , [62](#)
- prion diseases, [25](#), [34](#), [94](#)
- prognosis, disease, [102](#)
- progranulin (PGRN), [144](#), [187](#), [201– 203](#)
 - CSF levels, [144](#), [146](#)
 - gene mutations. *See* [GRN gene mutations](#)
 - serum levels, [144](#)
 - therapeutic targeting, [250– 251](#)
- progression, disease, [35– 36](#) , [102](#), [213](#)
- Progressive Aphasia Severity Scale (PASS), [230](#)
- progressive muscular atrophy (PMA), [69](#)
- progressive non-fluent aphasia (PNFA; nvPPA), [57– 59](#) , [92](#)
 - behavioral variant FTD vs., [133](#)
 - classification, [5](#), [6](#)
 - clinical presentation, [32– 33](#) , [57](#)
 - clinical syndrome, [18– 19](#)
 - core differential features, [61](#)
 - differential diagnosis, [33– 34](#)

- functional disability, [217– 218](#) , [219](#), [220](#)
- genetics, [62– 63](#)
- historical aspects, [4](#)
- imaging, [101](#), [132– 133](#) , [134](#)
- imaging–clinical correlations, [138– 139](#)
- neuropsychological testing, [117– 120](#)
- pathology, [7](#), [23](#), [57– 58](#) , [59](#), [181](#)
- PSP variant (PSP-PNFA), [85](#)
- progressive supranuclear palsy (PSP), [20](#), [82– 87](#)
 - biomarkers, [87](#)
 - clinical phenotypes, [84– 85](#)
 - clinicopathologic correlation, [23](#), [24](#)
 - corticobasal syndrome with (PSP-CBS), [85](#)
 - functional disability, [220](#), [221](#)
 - genetics, [84](#)
 - imaging, [86– 87](#)
 - parkinsonism with (PSP-P), [85](#)
 - pathology, [83– 84](#) , [168– 169](#)
 - pharmacotherapy, [233](#)
 - progressive non-fluent aphasia variant (PSP-PNFA), [85](#)
 - pure akinesia with gait freezing (PSP-PAGF), [85](#)
 - Richardson's syndrome (PSP-RS), [85](#), [168](#)
- prosopagnosia, [5](#), [20](#), [32](#)
 - imaging studies, [139](#)
- protein kinase inhibitors, [249](#)
- proteomic studies, [147– 148](#)
- PSP. *See* [progressive supranuclear palsy](#)
- psychiatric disorders
 - differential diagnosis, [34– 35](#) , [95– 98](#)
 - misdiagnosis, [229](#)
- psychiatric history, prior, [98– 99](#)
- Psycholinguistic Assessment of Language Processing in Aphasia (PALPA), [118](#), [119– 120](#)

psychotic/psychiatric symptoms
 atypical presentations with, [94](#)
 behavioral variant FTD, [31](#)
 C9orf72 mutations, [35](#), [73](#), [96](#)
 case study, [40](#)
 FTD-ALS, [20–21](#), [73](#)
 management, [231–232](#), [235–237](#)
pure progressive aphemia, [18](#)
Pyramids and Palm Trees (PPT) Test, [117](#)

quetiapine, [231](#), [246](#)

rapidly progressive dementias (RPD), [94–95](#)
reading deficits, [32](#), [59](#)
 imaging studies, [138](#)
reading tests, [56](#), [119–120](#)
relatives. *See* [family](#)
Repeat and Point Test, [117](#)
repeat-associated non-ATG (RAN) translation, [199](#), [252](#)
repetition tests, [56](#), [120](#)
research, [267](#), [269](#)
residential care, [238–239](#), [267](#)
retirement, early, [267](#)
Rey–Osterrieth complex figure test, [109](#)
Richardson's syndrome (PSP-RS), [85](#), [168](#)
rigid time-constrained routines, [217](#), [218](#), [225](#)
riluzole, [233](#)
risperidone, [232](#), [246](#)
rivastigmine, [245](#)

sagging brain syndrome, [95](#)
schizophrenia. *See also* [psychotic/psychiatric symptoms](#)
 ALS association, [73](#)
 differential diagnosis, [34–35](#), [97–98](#)

secondary prevention, familial FTD, [255](#)
seizure disorders, [95](#)
selective serotonin reuptake inhibitors (SSRIs), [37](#), [231](#), [244](#)
selegiline, [246](#)
semantic dementia (SD; svPPA), [59– 61](#) , [92](#)
 behavioral variant FTD vs., [133](#)
 case studies, [39– 40](#) , [225](#)
 classification, [5](#), [6](#)
 clinical presentation, [32](#), [59](#)
 clinical syndrome, [19– 20](#)
 core differential features, [61](#)
 differential diagnosis, [33– 34](#)
 functional disability, [216– 217](#) , [218](#), [219](#), [220](#)
 genetics, [62– 63](#) , [191– 192](#)
 historical aspects, [4– 5](#)
 imaging, [59](#), [60](#), [130– 132](#)
 imaging–clinical correlations, [138– 139](#)
 left temporal predominant, [5](#), [19](#), [39– 40](#) , [130– 131](#)
 neuropsychological testing, [117– 120](#)
 pathology, [7](#), [23](#), [181](#)
 prognosis, [102](#)
 right temporal predominant, [5](#), [39](#), [131](#)
semantic fluency test, [118](#)
semantic memory, [4](#)
 tests, [117– 118](#)
sentence–picture matching tasks, [56](#), [118](#)
septin 11 (SEPT11), [148](#)
sertraline, [244](#)
sex distribution, [92](#)
shopping, [214](#), [215](#), [217](#), [218](#)
single-photon emission computed tomography (SPECT), [125](#), [128– 130](#)
social activities, [217](#), [218](#), [235](#)
social cognition

behavioral variant FTD, [50](#)
 FTD-ALS, [72](#)– [73](#)
 imaging studies, [138](#)
 testing, [112](#)– [114](#)
 Social cognition and Emotional Assessment (SEA), [100](#), [115](#)
 Social Observer Behavior Checklist, [48](#)
 social relationships, disrupted, [266](#)
SOD1 gene mutations, [69](#), [77](#)
 sortilin (SORT1), [251](#)
 SPECT. *See* [single-photon emission computed tomography](#)
 speech disturbances
 FTD-ALS, [21](#), [71](#)
 imaging studies, [138](#)
 primary progressive aphasia, [18](#)
 progressive non-fluent aphasia, [32](#)– [33](#) , [57](#)
 speech-language pathologists (SLPs), [234](#)– [235](#)
 spinocerebellar ataxia, [180](#)
 Steele–Richardson–Olszewski syndrome. *See* [progressive supranuclear palsy](#)
 stereotyped behaviors, [46](#)– [47](#) , [236](#)
 stress granules, [203](#)– [204](#)
 Stroop Color and Word Test, [107](#)
 subcortical involvement
 behavioral variant FTD, [125](#), [126](#)
 corticobasal degeneration, [83](#), [170](#)
 FTLD with TDP-43 pathology, [172](#), [174](#)
 progressive supranuclear palsy, [83](#), [168](#)
 semantic dementia, [130](#)
 suberoylanilide hydroxamic acid (SAHA), [251](#)
 supranuclear gaze palsy, [85](#)
 survival rates, [36](#), [102](#)
 susceptibility genes, [190](#)– [191](#)
 symptomatic pharmacologic treatment, [37](#), [231](#)– [232](#) , [233](#), [243](#)– [248](#)
 synonym judgments task, [118](#)

TAF15 protein, [177](#), [178](#), [179](#), [180](#)

TARDBP mutations, [176](#), [190](#)

- animal models, [204–205](#)
- mutation frequency, [186](#)

tau, [83–84](#), [145](#), [199–200](#)

- CSF levels, [87](#), [145](#), [146](#)
- disease-specific markers, [87](#)
- isoforms, [83–84](#), [166](#), [167](#)
- monoclonal antibodies, [249–250](#)
- normal expression and function, [165–166](#)
- pathologic forms, [166–167](#), [168](#)
- pathophysiology, [171](#), [199–200](#), [201](#)
- phosphorylated. *See* [phosphorylated tau](#)
- therapeutic targeting, [248–250](#)
- vaccines, [249](#)

tau 33 kDa/55 kDa ratio, CSF, [87](#)

tau gene. *See* [MAPT gene](#)

tau positron emission tomography (PET), [100–101](#), [255](#)

tau-positive inclusions, [6](#)

- corticobasal degeneration, [170](#)
- FTDP-17, [7](#)
- FTLD with. *See* [frontotemporal lobar degeneration with tau-positive inclusions](#)
- globular glial inclusions, [170](#)
- MAPT* mutations, [170](#)
- Pick's disease. *See* [Pick bodies](#)
- progressive supranuclear palsy, [168](#)

tauopathies. *See* [frontotemporal lobar degeneration with tau-positive inclusions](#)

taxanes, [250](#)

TDP-43, [144](#), [172](#), [200–203](#)

- CSF levels, [144](#), [146](#)
- gene mutations. *See* [TARDBP mutations](#)
- in disease, [172](#)

mouse models, [253– 254](#)
pathologic forms, [172](#), [174](#)
pathophysiology, [177](#), [202](#), [203– 204](#)
plasma levels, [144](#)
therapeutic targeting, [250](#)
TDP-43 pathology, [6](#), [172](#), [173](#)
 FTLD with. *See* [frontotemporal lobar degeneration with TDP-43 pathology](#)
 other neurodegenerative diseases, [176– 177](#)
telephone use, [215](#), [218](#), [219](#)
temporal lobe atrophy
 behavioral variant FTD, [125– 126](#) , [128](#)
 FTD-ALS, [130](#), [131](#)
 Pick's original cases, [1– 2](#)
 semantic dementia, [5](#), [19](#), [59](#), [130– 132](#)
temporal lobe seizure disorders, [95](#)
terminology
 diagnostic, [102](#)
 disease, [2– 3](#) , [15– 16](#) , [91](#), [92](#)
theory of mind (ToM) deficits
 behavioral variant FTD, [50](#)
 FTD-ALS, [72](#)
 testing, [112– 113](#)
Theory of mind cartoons, [113](#)
Theory of mind stories, [113](#)
tideglusib, [249](#)
TMEM106B gene, [190](#)
tolcapone, [233](#)
topiramate, [247](#)
Tower of London Test, [111](#)
TPI-287, [250](#)
Trail Making Test, [107](#), [111](#)
transactive response DNA-binding protein 43. *See* [TDP-43](#)
transcortical sensory aphasia, [4](#), [19](#)

transgenic mouse models, [171](#), [200](#), [205](#), [253– 254](#)
transmissible spongiform encephalopathies. *See* [prion diseases](#)
transportin 1 (Trn1), [177](#), [179](#), [180](#)
trazodone, [37](#), [231](#), [244](#)
treatment, [37](#)
 pharmacologic. *See* [pharmacologic therapy](#)
 symptomatic, [232](#)
tumor necrosis factor- α (TNF- α), [201– 203](#) , [251](#)

ubiquitin-positive pathology. *See* [frontotemporal lobar degeneration with
 ubiquitin-positive pathology](#)
utilization behavior, [17](#)

valproic acid, [247](#)
vascular dementia (VaD), [24– 25](#) , [34](#)
VCP mutations, [189](#), [205](#)
 animal models, [205](#)
 mutation frequency, [186](#)
 neuropathology, [176](#), [189](#)
 pathophysiology, [177](#), [189](#), [205](#)
verbal fluency deficits
 behavioral variant FTD, [48](#)
 FTD-ALS, [70– 71](#)
 logopenic progressive aphasia, [61](#)
 progressive non-fluent aphasia, [57](#)
 testing, [110– 111](#)
verbal fluency index (Vfi), [70](#), [71](#)
Visual Object and Space Perception Test (VOSP), [109](#)
visuospatial function, [49](#)
 testing, [109– 110](#)

Western Aphasia Battery, [56](#)
white matter degenerative diseases, [95](#)
Wilson's disease, [95](#)

Wisconsin Card Sorting Test, [111](#)

word fluency tests, [110](#)– [111](#)

Word Picture Matching task, [118](#)

Words and Sentences Repetition test, [120](#)

zebra fish, [199](#), [254](#)

Mục lục

Half title	2
Title page	3
Imprints page	4
Epigraph	6
Contents	7
Contributors	10
Editor biographies	16
Foreword	21
Preface	23
Section 1 Introduction to and brief history of FTD	30
Chapter 1 Historical introduction to FTD	31
Introduction	31
What did Arnold Pick actually describe?	32
Rediscovering Pick's disease: from dementia of the frontal type and progressive aphasia to frontotemporal dementia	35
Progressive aphasia and semantic dementia	38
Frontotemporal dementia and frontotemporal lobar degeneration	42
Familial chromosome 17-linked frontotemporal dementia and the discovery of unique tau pathology	46
Frontotemporal dementia with motor neuron disease	48
Discovery of the C9orf72 mutation	50
Corticobasal syndrome	50
Conclusions	51
References	51
Chapter 2 Overview of frontotemporal dementia and its relationship to other neurodegenerative disorders	70
Introduction to terminology and historical aspects	70
Clinical syndromes of FTD/Pick complex and their assessment	74
Frontotemporal dementia: behavioral variant (bvFTD)	74
Primary progressive aphasia (PPA)	78

Semantic dementia (svPPA, semantic aphasia)	80
Logopenic variant of PPA (lvPPA)	82
Corticobasal degeneration (CBD) and progressive supranuclear palsy PSP)	82
Motor neuron disease and FTD (FTD-MND)	84
Neuropathology and molecular genetics	85
Pathology	85
Genetic relationships	89
Clinicopathologic correlations in FTD/Pick complex	90
Differential diagnosis	92
Alzheimer's disease	92
Vascular dementia	94
Prion disease	94
Psychiatric phenocopies	95
Conclusions	96
References	97
Section 2 Clinical phenotypes	108
Chapter 3 Overview of frontotemporal dementia and the variety of its clinical presentations	109
Introduction	109
Epidemiology	111
Classical features of frontotemporal dementia spectrum syndromes	111
Behavioral variant FTD (bvFTD)	111
Semantic dementia (SD)	114
Progressive non-fluent aphasia (PNFA)	116
Atypical presentations and the differential diagnosis of FTD	117
Differentiating FTD from Alzheimer's disease	117
Differentiating FTD from other neurodegenerative conditions	120
Differentiation from cerebrovascular disease	120
Differentiation from psychiatric conditions	121
Clinical course	123
Managing FTD	125

Caregivers	126
Patients	127
The future	129
Case studies	129
References	136
Chapter 4 Behavioral variant frontotemporal dementia	145
Introduction	145
Diagnosis of bvFTD	148
Behavior in bvFTD	151
Behavioral disinhibition	151
Apathy and inertia	152
Loss of empathy	153
Perseverative, stereotyped, and compulsive behaviors	154
Hyperorality and dietary changes	154
Measuring behavior in bvFTD	155
Cognition in bvFTD	157
Executive and generation deficits	158
Relative preservation of visuospatial and constructional abilities	159
Relative preservation of episodic memory	160
Measuring cognition in bvFTD	161
Emotion, social cognition, and decision-making in bvFTD	161
Emotion and social cognition	162
Decision-making	164
Experimental tasks in clinical practice	165
Conclusions	165
Acknowledgment	166
References	166
Chapter 5 Primary progressive aphasia	176
Introduction	176
The role of neuropsychological assessment	178
The variants of primary progressive aphasia	181
Non-fluent/agrammatic variant of primary progressive aphasia	181

Semantic variant of primary progressive aphasia	185
Logopenic/phonologic variant of primary progressive aphasia	189
Atypical and mixed cases of primary progressive aphasia	193
Genetic studies	194
Treatment and management	195
References	195
Chapter 6 The FTD-ALS spectrum	206
FTD-ALS spectrum: the evolution of the concept	206
Profile of cognitive change in FTD-ALS	210
Executive dysfunction in FTD-ALS	212
Language dysfunction in FTD-ALS	215
Social cognition in FTD-ALS	218
Behavior change in FTD-ALS	219
Psychiatric symptoms in FTD-ALS	220
Assessing cognitive and behavior dysfunction in FTD-ALS	221
Brain imaging and cognition in FTD-ALS	224
Pathology of FTD-ALS	226
Genetics of FTD-ALS	227
Conclusions	228
References	229
Chapter 7 Progressive supranuclear palsy and corticobasal degeneration in the FTD spectrum	240
Introduction	240
Neuropathology and genetics of PSP and CBD	243
Clinical phenotypes associated with PSP and CBD	246
Brain imaging in PSP and CBD	250
Biomarkers for the diagnosis of PSP and CBD	253
Conclusions	254
References	254
Section 3 Approach to the diagnosis of FTD	264
Chapter 8 Overview of clinical assessment of frontotemporal dementia syndromes	265
Introduction	265

Clinical characteristics of FTLD spectrum diseases	270
Major FTLD clinical syndromes	272
Other clinical phenotypes	272
Differential diagnosis of FTLD	273
Differential diagnosis with diseases traditionally considered “neurologic”	274
Differential diagnosis with diseases traditionally considered “psychiatric”	276
Diagnostic assessment	283
History of symptoms	283
The office-based cognitive examination	286
The neurologic examination in suspected FTLD syndromes	287
Neuropsychological testing in FTLD syndromes	287
Neuroimaging, fluid biomarkers, and other diagnostic tests	288
Clinical course of FTD: the value of longitudinal reassessment of diagnostic classification	291
A recommendation for the diagnostic terminology used in FTLD	292
References	293
Chapter 9 Neuropsychological assessment of frontotemporal dementia	304
Behavioral variant FTD	305
Screening tests	305
Attention	306
Memory	308
Visuospatial function	312
Executive functions	314
Frontal screening tools	314
Classical executive function tests	315
Social cognition tests	319
Theory of mind tests	319
More complex ecologically valid executive function tests	323
Language	329
Language variants of FTD	329

Semantic memory	329
Semantic fluency	332
Synonym judgments	332
Naming	333
Reading	335
Repetition	336
Oral production	336
Conclusions	337
References	337
Chapter 10 Imaging of frontotemporal dementia	349
Clinical syndromes	350
Behavioral variant FTD (bvFTD)	350
Frontotemporal dementia with motor neuron disease/amyotrophic lateral sclerosis (FTD-MND/ALS)	359
Primary progressive aphasia (PPA)	361
Semantic variant PPA (svPPA)	361
Non-fluent variant PPA (nfvPPA)	364
Logopenic variant PPA (lvPPA)	366
Other forms of PPA	368
Comparison of bvFTD and the PPA syndromes	368
Genetic syndromes	369
Pathologic syndromes	373
Comparison of FTD with other neurodegenerative disorders	374
Brain-behavior correlation	375
Behavioral variant FTD	375
Primary progressive aphasia	376
References	378
Chapter 11 Cerebrospinal fluid biomarkers of frontotemporal lobar degeneration	389
Introduction	390
Hypothesis-driven CSF research in FTLD	391
Progranulin and TDP-43 in CSF of FTLD patients	391
CSF tau and P-tau in FTLD patients	393
CSF amyloid in FTLD patients	400

Neurofilaments in FTLD patients	403
Non-hypothesis-driven research in FTLD: biomarker discovery	403
Summary	405
References	405
Chapter 12 Genetic counseling for FTD	417
Introduction	417
Conclusions	442
References	444
Section 4 Pathology and pathophysiology	446
Chapter 13 Neuropathology of frontotemporal dementia and related disorders	447
Introduction	447
FTLD-tau	450
Normal tau expression and function	451
Tau in disease	454
Neuropathologic subtypes of FTLD-tau	455
Pick's disease	456
Progressive supranuclear palsy	458
Corticobasal degeneration	459
Globular glial tauopathies	460
FTD and parkinsonism caused by MAPT mutations	461
Other tauopathies	462
Models and pathogenic mechanisms	463
FTLD-TDP	464
Normal TDP-43 expression and function	464
TDP-43 in disease	465
Pathologic subtypes of FTLD-TDP	469
FTLD-TDP type A	470
FTLD-TDP type B	471
FTLD-TDP type C	471
FTLD-TDP type D	471
Familial FTLD-TDP	471
FTLD-TDP due to GRN mutations	471

FTLD-TDP due to C9orf72 repeat expansion mutation	472
FTLD-TDP due to VCP mutations	475
FTLD-TDP due to TARDBP mutations	475
TDP-43 pathology in other neurodegenerative disease	475
Pathogenesis of FTLD-TDP	476
FTLD-FET	477
Normal FET expression and function	478
FET proteins in disease	478
FTLD-FET subtypes	480
Atypical FTLD-U	481
Neuronal intermediate filament inclusion disease	482
Basophilic inclusion body disease	483
FET proteins in other neurodegenerative diseases	484
FTLD-FET pathogenesis	484
FTLD-UPS	485
Other pathologic causes of FTD	486
Molecular correlates of FTD phenotypes	487
Conclusions	488
References	488
Chapter 14 Genetics of frontotemporal dementia and related disorders	497
Introduction	498
Mendelian FTLD genes	499
MAPT	499
GRN	504
C9orf72	506
VCP	509
CHMP2B	510
Mendelian ALS genes TARDBP and FUS	511
Susceptibility genes and risk loci in FTLD	512
TMEM106B	512
Risk variations in Mendelian FTLD genes	513
Concluding remarks	514
Note	517

Acknowledgments	519
References	519
Chapter 15 Pathophysiology and animal models of frontotemporal dementia	530
C9ORF72	531
Pathophysiology	532
Animal models	535
Tau	535
Pathophysiology	535
Animal models	537
Progranulin	544
Pathophysiology	544
Animal models	546
TDP-43 and FUS	546
Pathophysiology	547
Animal models	549
VCP	550
Pathophysiology	551
Animal models	551
CHMP2B	552
Pathophysiology	552
Animal models	552
Conclusions	553
References	553
Section 5 Treatment	566
Chapter 16 Functional disability and the impact of frontotemporal dementia in everyday life	567
How activities of daily living are defined and evaluated	568
Patterns of functional impairment in FTD subtypes, and their progression	575
Behavioral variant FTD	576
Primary progressive aphasia: semantic variant	583
Primary progressive aphasia: non-fluent variant	592
Primary progressive aphasia: logopenic variant	593

Corticobasal degeneration and progressive supranuclear palsy	595
Relationship between cognitive deficits and behavioral changes with ADLs	596
Impact of functional disability and disease progression on family carers	598
Improving functional abilities in FTD: therapeutic recommendations	602
Conclusions/summary	606
Cases	606
References	609
Chapter 17 Practical management of frontotemporal dementia	618
Initial clinic contact and early-stage management	618
Management at middle stages	622
Pharmacologic management	623
Non-pharmacologic interventions	630
Cognitive impairments	631
Communication impairments	632
Motor impairments	634
Behavioral disturbances and neuropsychiatric impairments	634
Management at advanced stages	643
Conclusions	645
References	646
Chapter 18 Pharmacologic therapy for FTD and related disorders	654
Introduction	654
Neurotransmitter-based symptomatic treatments	655
Antidepressants	656
Acetylcholinesterase inhibitors	659
Antipsychotics and dopaminergic therapies	661
Anti-epileptics	665
Memantine	666
Parkinsonism treatment	668
Potential disease-modifying treatments	669
Targets	669
Tau	669

Tau gain-of-function therapies	671
Tau loss-of-function therapies	672
TDP-43	673
Progranulin	674
Immunogenicity	676
C9ORF72	677
Models	680
Pluripotent stem cells	681
Mouse	681
Other	683
Future directions	683
Industry cooperation	685
Clinical trial considerations	685
Conclusions	688
References	688
Chapter 19 The family's perspective on FTD	703
Stage I. Something is wrong	708
Stage II. Maybe there is a medical problem	709
Stage III. A series of medical professionals and opinions/diagnoses	710
Stage IV. Referral to a physician familiar with FTD	711
Stage V. The diagnosis is FTD	711
Managing the disease through partnership	712
Avoid nihilism after the diagnosis	713
Identify a collaborative team	714
Recognize the impact of disrupted social relationships and obligations among younger individuals	715
Suggest anticipatory legal and financial planning	716
Assist with community placement	717
Discuss research opportunities	718
Creating a broader community for resources and support	718
AFTD initiatives and programs	721
Promoting and funding research	722
Supporting and informing families	723

Educating medical and healthcare professionals	724
Promoting awareness	724
Advocating for support and research funding	725
Facilitating international partnerships	725
A force for change	726
Index	729